Neuroplasticity

New Biochemical Mechanisms

JA Costa e Silva • JP Macher • JP Olié

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NEUROPLASTICITY

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Editors-in-chief

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Jean-Paul Macher is a psychiatrist and researcher in Clinical Neurosciences. Dr Macher's main research areas are neuropsychopharmacology and functional brain imaging. He is a member of numerous societies in France, Europe and America, including the European College of NeuroPsychopharmacology (ECNP), Association of European Psychiatrists (AEP), Association Française de Psychiatrie Biologique (AFPB), Society for Mathematical Psychology (SMP), American Psychiatric Association (APA), Australasian Society of Biological Psychiatry (ASBP), European Sleep Research Society (ESRS), and the Chilean Association of Neurology, Psychiatry and Neurosurgery. Dr Macher is an expert

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Eberhard Fuchs is Professor for Neurobiology at the Department of Neurology, Medical School, University of Göttingen and head of the Laboratory of Clinical Neurobiology at the German Primate Center, Göttingen. He received is PhD from the University of Munich in Biology and joined the German Primate Center in 1982. In 2002 Dr Fuchs was the first awardee of the prestigious Science Award donated by the Stifterverband für die Deutschen Wissenschaft (Germany's Donors' Association for Sciences and Humanities) for his studies on the effect of antidepressants within neuronal networks.

As a neurobiologist, Dr Fuchs is interested in functional neuroanatomical, neuropharmacological, electrophysiological, behavioral and molecular approaches to investigate functioning of the brain in animal models of mood

disorders. The aim of his work is to elucidate brain structures, circuits, pathways and mechanisms that underlie normal and pathological behavior. This work integrates inputs from other research fields with the ultimate aim of developing and testing new therapeutic strategies for psychiatric disorders such as depression. Studies from Dr. Fuchs' laboratory have substantially contributed to the formulation of the neuroplasticity hypothesis of depression. These findings represent major advances in our understanding of the effects of antidepressants and provide a framework for the development of novel therapeutic agents.

Lawrence Reagan is an Associate Professor in the Department of Pharmacology, Physiology and Neuroscience at the University of South Carolina School of Medicine and currently serves as the Graduate Director for the Neuroscience Focus Group at the USC School of Medicine. Dr Reagan received his PhD from the Department of Pharmacological Sciences at the University of Pennsylvania School of Medicine in 1995. He performed postdoctoral studies at The Rockefeller University, where he later served as a Research Associate Professor and currently holds an adjunct faculty appointment. He joined the faculty at the USC School of Medicine as an Assistant Professor in 2002 and was promoted to Associate Professor in 2008. Dr Reagan's laboratory is interested in the plasticity of limbic structures such as the hippocampus and amygdala under physiological conditions, as well as how neuroplasticity may be impaired in the hippocampus and amygdala under stress conditions. More specifically, Dr. Reagan's laboratory investigates the impact of stress upon the glutamatergic system in the hippocampus and amygdala. These studies revealed that stress can adversely affect the expression of components of the glutamate synapse, including glutamate receptors and glutamate transporters, effects of stress that may be inhibited by antidepressant treatments. In collaboration with **Jim Fadel** and **Leah Reznikov** at the USC School of Medicine, Dr Reagan's studies have determined that stress and antidepressant treatments differentially modulate glutamate neurotransmission in the hippocampus and amygdala. Moreover, prior stress history also differentially impacts glutamatergic responses to acute stress in these limbic structures. Collectively, Dr Reagan's studies suggest that impairments in the glutamatergic system are among the mechanisms through which stressful life events contribute to the etiology and progression of mood disorders like depressive illness.

Bruce McEwen is the Alfred E. Mirsky Professor and Head of the Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology at The Rockefeller University, where he was first appointed professor in 1981. He is a member of the US National Academy of Sciences, the Institute of Medicine, the American Academy of Arts and Sciences and a Fellow of the New York Academy of Sciences. He served as Dean of Graduate Studies from 1991–1993 and as President of the Society for Neuroscience in 1997–1998. As a neuroscientist and neuroendocrinologist, Prof. McEwen studies environmentally regulated, variable gene expression in brain mediated by circulating steroid hormones and endogenous neurotransmitters in relation to brain sexual differentiation and the actions of sex, stress and thyroid hormones on the adult brain, and his laboratory combines molecular, anatomical, pharmacological, physiological and behavioral methodologies and relates their findings to human clinical information. His laboratory discovered adrenal steroid receptors in the hippocampus in 1968. He is a member of the MacArthur Foundation Research Network on Socioeconomic Status and Health, in which he is helping to reformulate concepts and measurements related to stress and stress hormones in the context of human societies. He is the co-author of a book for a lay audience with science writer Harold M Schmeck, Jr, called *The Hostage Brain* (Rockefeller University Press, 1994), and another book with science writer Elizabeth N. Lasley called *The End of Stress as We Know It* (Joseph Henry Press and the Dana Press, 2002). He is a recipient of the American Psychological Association Award for Distinguished Scientific Contributions in 2003, as well as the Karl Spencer Lashley Award, American Philosophical Society and the Pat Goldman Rakic Award, National Association for Research on Schizophrenia and Affective Disorders in 2005 and the Pasarow Foundation Neuropsychiatry Award in 2006.

Thérèse Jay is a director of research appointed at INSERM, the French National Institute of Mental Health. Since 2003, she has been the group leader of "Neuronal Plasticity and Psychiatric Disorders" at INSERM U796 (Laboratory of Pathophysiology of Psychiatric Diseases, University Paris Descartes) at Sainte Anne Hospital, Paris. Since January 2008, she is the Co-Director of the main group "Pathophysiology of Psychiatric Diseases" (INSERM, Univ Paris Descartes, Sainte Anne Hospital) where most research projects are now developed as translational. Thérèse Jay was first appointed as a research scientist at the College de France in

Paris after having received an award from the National Institute of Mental Health to accomplish a 3-year postdoctoral program in the USA (Bethesda, MD). She has been the recipient of awards (international fellowships) in her research field over the years that have allowed her to work abroad (the Netherlands, Japan, the USA) and received support to set up her own research group. She is presently a scientific advisor and the French representative at the European Cooperation in the field of Scientific and Technical Research. She was recently named as a coordinator of a neuroscience panel in Europe. She holds the membership of prestigious professional societies (Society for Neuroscience, French Society for Neurosciences, CINP, ECNP). She also works as an editorial consultant on high ranked international journals and serves on the Editorial Committee of *The European Journal of Psychiatry and Frontiers in Neuroscience*. Thérèse Jay has coauthored more than 80 articles, review articles and book chapters on neuroscience and biological psychiatry. She is the coordinator (PI) of several public and private grants and is regularly invited to give seminars abroad. Thérèse Jay has organized a number of symposia in different international meetings.

Philip Gorwood studied medicine from 1982–1988, specializing in psychiatry, then became a resident of Paris hospitals until 1992. As a full-time researcher at the INSERM Genetic Epidemiology unit he became MD (1992), psychiatrist (1992), with a PhD in genetics (1996), and was appointed as Research Supervisor in 1999 and Professor of Psychiatry in 2004. In 1992, Prof. Gorwood received the Lilly "First Communication" award, and later on the Organon/French Association for Biological Psychiatry "Best Communication of the Year 1997" award. In 1999, he received the Association of European Psychiatry young researcher award; and in 2000, the French National Academy of Medicine award for the best research against alcohol-dependence. Since 1992, he has published 80 papers and 24 book chapters, and serves on 16 editorial boards for psychiatry, neuroscience and genetics journals published in English. He recently edited a book entitled '*Psychopharmacogenetics*' (Springer, 2006). The main topics of Prof. Gorwood's research are related to vulnerability to psychiatric and addictive disorders, including genetic factors. Prof. Gorwood became head of a research unit at the INSERM in Paris, devoted to phenotypical and genetic researches on psychiatric and addictive disorders. He is now Co-Editor in Chief of the journal *European Psychiatry*.

FOREWORD

In 2004, when we published the first edition of *Neuroplasticity*, a completely new approach to the pathophysiology of depression was being created, and was promising to revolutionize the way we conceptualize depressive disorders and manage depressed patients. Since then, there have been many advances in our understanding of the pathophysiology of depression, and recent studies have provided evidence that structural remodeling and functional alterations of certain brain regions are indeed a fundamental feature of depressive illness. This has given rise to the neuroplasticity hypothesis, which, in turn, has opened up a new era in the study of affective disorders and new opportunities for the development of treatments. In this completely revised second edition of *Neuroplasticity — New Biochemical Mechanisms*, we explore the most recent advances in our understanding of the mechanisms underlying neuroplasticity and the implications for the treatment of depression.

As described by Eberhard Fuchs (Göttingen, Germany), the neuroplasticity hypothesis arose from the observation that hippocampal shrinkage is a feature of many neuropsychiatric disorders, including stress and depression. Moreover, these neuronal changes appear to extend beyond the hippocampus into the entire limbic–cortical–striatal–pallidal–thalamic tract. This led to the view that an effective antidepressant therapy should act by restoring structural as well as functional alterations in neural circuits, and support the adaptive neuroplasticity that underlies normal brain function.

As regards the role of neurotransmitters, a growing body of data now suggests that the glutamatergic system is important in the pathophysiology and treatment of mood disorders. Glutamate is also known to play a major role in neuronal plasticity and cellular resilience. Progress in this field is discussed by Lawrence P. Reagan (South Carolina, USA) and his coworkers. They conclude that current evidence suggests that glutamate transmission in the central nervous system may be of key clinical significance as a promising novel therapeutic target.

The changes in the glutamatergic system in clinical depression are also associated with changes in AMPA receptor function, and these may be inhibited by antidepressant treatment. Using the example of the antidepressant,

tianeptine, Bruce S. McEwen (New York, USA) explores the relationship between antidepressant mechanisms of action and expression of glutamate receptors.

Thérèse M. Jay (Paris, France) takes these arguments one step further in her discussion of cellular plasticity and its links to the pathophysiology of depression. She demonstrates that some atypical antidepressants, particularly tianeptine, promote and restore neuroplasticity and cellular resistance to the neuropathological changes that accompany depression, thereby preventing functional and structural alterations that increase vulnerability to depression and promote its progression.

In the final contribution to this book, Philip Gorwood (Paris, France) comments on the clinical implications of these advances. Understanding the important role of neurotoxicity for the pathophysiology of depression and that of neuroplasticity in the efficacy of antidepressant treatment may also give meaning to the typical outcome of major depressive episodes, i.e. the risk of subsequent episodes and the length and quality of remission.

In reviewing the most important advances, this second edition of *Neuroplasticity* provides an updated view of this exciting area of research via contributions from leaders in the field. Our aim is to aid understanding of both the mechanisms underpinning the depressive episode and the potential of antidepressant therapies that modulate neuroplasticity.

NEUROPLASTICITY – A NEW APPROACH TO THE PATHOPHYSIOLOGY OF DEPRESSION

Eberhard Fuchs

I Introduction

All available antidepressive-acting molecules are based on the empirical discoveries of the clinical efficacy of two classes of compounds, the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors, that have now been used for more than half a century. These compounds have been shown to overcome deficits in serotonin, noradrenaline and possibly dopamine function in the brain. This finding formed the basis for the monoamine hypothesis of depression [1] and subsequent monoamine receptor hypotheses proposing that depressive disorders are caused by a chemical imbalance in the brain, which can be counteracted and corrected by antidepressants. The role of monoamines has long been a central focus of research efforts, and resulted in the development of newer and more specific antidepressant agents, the monoamine reuptake inhibitors, which have the same core mechanisms of action in that they promote central monoaminergic neurotransmission.

Although the monoaminergic neurotransmitters are undoubtedly involved in the pathophysiology of depression and the monoamine hypothesis has since been refined and extended, it is now increasingly recognized that monoamine deficits are only part of the depression story and that raised levels of brain monoamines are not sufficient on their own to explain the mechanism of action of antidepressants (for review, see Castren, 2005 [2]).

In extension to the chemical hypothesis of depression, contemporary theories suggest that major depressive disorders may be associated not only with an imbalance in brain neurotransmitters and neuromodulators but also with an impairment of neuroplasticity and cellular resilience, and that antidepressant medications act by normalizing this impairment [3–6]. Notably, the cellular processes mediating brain adaptation are now seen as potential vulnerabilities underlying neuropsychiatric disorders. Neuroplasticity is the term widely used to describe changing brain functioning at all levels of neural organization, from genetic to cellular and behavioral parameters.

II From neurotransmitter deficits to neuroplasticity – the evolution of a concept

Approximately one century ago, it was generally established that the brain consists of neural cells, neurons and glia, and forms a cellular rather than a continuous network. Based on the work of the Spanish anatomist Ramon y Cajal, a rather static view of the brain has prevailed in which electrical and chemical information was thought to be processed through a fixed system of neuronal circuits [7]. In recent years, however, this view has been gradually revised on the basis of various studies showing that neural circuits and connections are subject to lifelong modifications and reorganizations. This ability of the brain to undergo functionally relevant adaptations following external and/or internal stimuli is generally referred to as neural plasticity. The dynamic processes that constitute neural plasticity are based on the capacity of neural systems, brain nuclei, single neurons, synapses, and receptors to adapt and change their structural and functional repertoire in response to alterations in the internal and/or external environment. Neural plasticity is absolutely necessary for adequate functioning of an individual in the continuously changing environment.

Even under normal and undisturbed conditions, contacts between neurons are continuously replaced and renewed in the adult and differentiated brain (Figure 1). Enhanced axonal outgrowth and collateral sprouting on the presynaptic site may lead to the formation of new synapses and existing ones may be eliminated by terminal retrograde degeneration. The number of postsynaptic sites can be increased or decreased by alterations in the size of the dendritic tree or its spine density, or through changes in glial organization. Steroid hormones released from the gonads, adrenals and thyroid gland seem to play a particular role as triggers of such structural reorganization within the brain. Through their transcriptional activity, these hormones regulate gene expression in the neural cells [8]. An impressive example of steroid-mediated reorganization of neuronal connectivity in the adult brain is the fluctuation of synaptic contacts in different brain areas of female rats during the menstrual cycle [9]. It has been shown in the brains of ground squirrels that as a consequence of changes in sensory inputs and in circulating hormones, synaptic contacts of mossy fibers with CA3 hippocampal pyramidal neurons are altered in many aspects of their structure during different stages of the torpor-activity cycle

[10]. Moreover, dendritic shrinkage of hippocampal CA3 pyramidal neurons was reported after chronic stress exposure or as a result of corticosterone administration [11–14].

However, structural changes in neurons are not only restricted to the hippocampus but have also been demonstrated in the rat prefrontal cortex, where pyramidal cells have been shown to react to chronic stress by retracting their dendrites and by spine loss, with these changes being tightly linked to the daily periods of resting and activity [15,16]. However, using morphometric techniques, Vyas et al. [17] have demonstrated that chronic stress has totally different effects on dendritic remodeling in rat amygdaloid neurons. In striking contrast to the findings in the hippocampus and prefrontal cortex, chronic immobilization stress resulted in increased dendritic arborization of neurons in the basolateral nucleus of the amygdala (BLA). This stress-induced enhancement in dendritic arborization did not represent a generalized increase in all classes of BLA neurons, but was restricted only to pyramidal

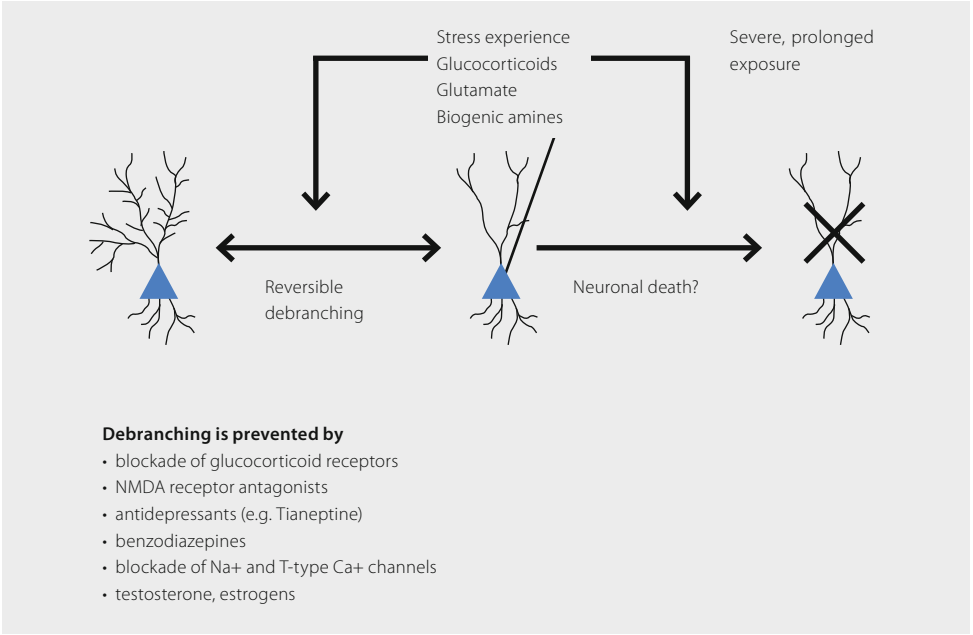

Figure 1. Chronic stress, excess concentrations of glutamate, biogenic amines and glucocorticoids affect the morphology of hippocampal CA3 pyramidal neurons, resulting in a pronounced debranching of apical dendrites. This effect can be blocked or counteracted by different compounds including established antidepressant drugs. Note that a significant loss in the number of pyramidal neurons following exposure to stress or hypercortisolemia can be excluded.

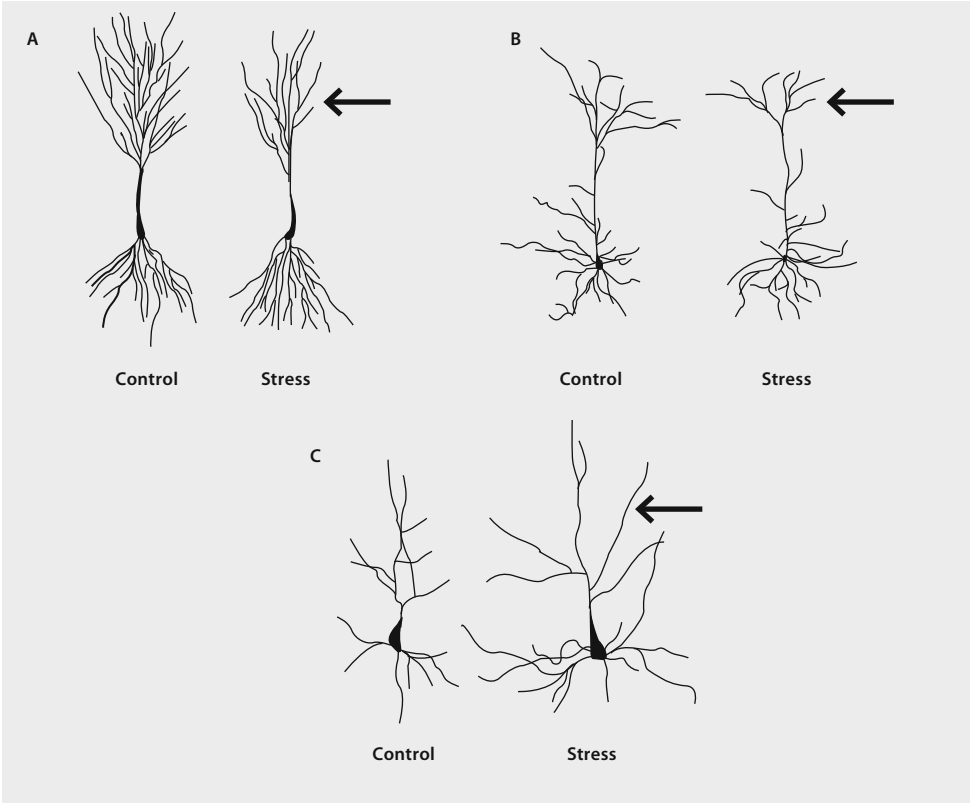

Figure 2. Morphological changes as a consequence of stress exposure are not restricted to the hippocampus but have also been demonstrated in the prefrontal cortex and amygdala.
In the hippocampus and the prefrontal cortex, chronic stress results in a significant retraction of dendrites and spine loss, and these changes are tightly linked to the daily periods of resting and activity. In clear contrast to what is observed in the hippocampus and the prefrontal cortex, chronic stress increased the dendritic arborization of pyramidal and stellate neurons in the basolateral nucleus of the amygdala.
A Chronic psychosocial stress causes apical dendritic debranching of hippocampal CA3 pyramidal neurons in subordinate tree shrews. With modifications from Magariños et al. [13].
B Chronic immobilization stress results in a significant shrinkage of apical dendrites of pyramidal neurons in prefrontal cortical layer III. With modifications from Perez-Cruz et al. [15].
C In amygdaloid stellate neurons, chronic immobilization stress increases dendritic arborization. With modifications from Vyas et al. [17].
Arrows indicate areas of interest.

and stellate neurons, which are presumably excitatory projection neurons. These morphological alterations (Figure 2) reflect the capacity of the adult brain to reorganize and adjust its neuronal circuits in response to altered hormonal and/or sensory inputs and mirror presumptive changes in neuronal communication.

III Depression and reduced hippocampal volume

However, not all processes of neural plasticity are beneficial, as demonstrated by the altered structure and function observed in the brains of patients with mood disorders. Probably the most reproduced finding from numerous in vivo magnetic resonance imaging (MRI) studies is a small but significant (10–15%) reduction in hippocampal volume of depressed patients. Moreover, the duration of the depressive episodes is closely paralleled by the volumetric changes, with longer periods of depression generally corresponding to smaller hippocampi [18]; for further references see Czéh & Lucassen, 2007 [19]. Treatment with antidepressants significantly improved hippocampal function (e.g. memory), but did not always result in altered hippocampal volume. Even though the possibility cannot be excluded that a smaller hippocampus might be a trait characteristic of major depressive disorder, it should be mentioned that hippocampal shrinkage is not specific to depression and has been reported in various other neuropsychiatric and neurological disorders, including posttraumatic stress disorder (PTSD), schizophrenia, dementia, Alzheimer's, Parkinson's and Huntington's disease, epilepsy and chronic alcoholism [19].

The exact mechanisms responsible for the hippocampal volume loss have not been identified yet. Significant neuronal loss following exposure to repeated episodes of hypercortisolemia can be excluded, as no major cell loss was apparent in human post mortem brain tissue of severely depressed patients, nor was any neuropathology detectable. In addition, apoptosis was observed only to a very limited extent in depressed patients. This is consistent with other studies that failed to find obvious neurotoxic effects of hypercortisolemia or chronic stress on the hippocampus of other species including non-human primates [19].

Because stressful life events are associated with an increased risk of developing depression, preclinical studies in which animals are exposed to chronic stress have been used to understand the cellular mechanisms underlying hippocampal shrinkage in depressed patients. On the basis of morphometrical studies, parameters such as alterations in somatodendritic, axonal, and synaptic components, suppressed adult neurogenesis, and changes in glial cell numbers have been suggested as major causative factors for hippocampal shrinkage (Figure 3) [19]. It should be noted, however, that in the only report on post mortem hippocampal samples from psychiatric

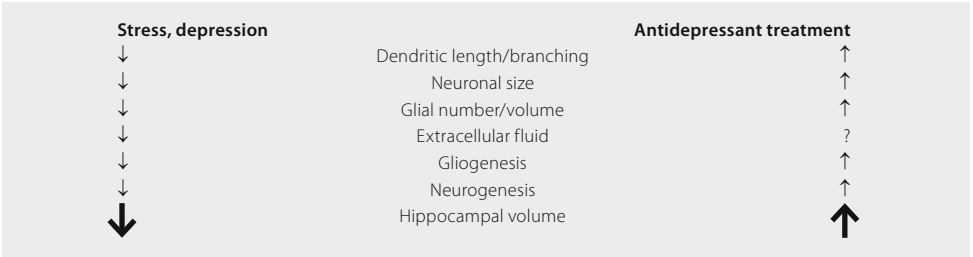

Figure 3. Proposed mechanisms leading to reduced hippocampal volume and the effect of antidepressant treatments. Stress-induced cellular changes observed in animal studies suggest various processes that could underlie hippocampal shrinkage as a consequence of depressive disorders. Dendritic shrinkage and debranching as a result of chronic stress have been repeatedly documented in preclinical studies. A reduction in cellular size has been reported for both neurons and glia. A reduced number of astroglia after chronic stress has been reported in an animal study. Clinical data indicate that shifts in extracellular fluid between brain tissue and the ventricles may contribute to the hippocampal volume reduction. In animal studies, reduced gliogenesis has been reported after stress exposure. A reduction in hippocampal dentate neurogenesis has been suggested to play a major role in hippocampal shrinkage. However, these cellular changes are too small to be relevant modulators of the significant changes in volume of the entire hippocampus. Results from animal studies indicate that many of the stress-induced cellular changes can be reversed by antidepressant treatment.

patients that exists so far, investigators failed to find any change in neurogenesis in the depressed patients [20]. However, as this study was based on a relatively small sample size, further studies are warranted.

Recent animal studies revealed that various antidepressant treatments including electroconvulsive therapy may counteract those cellular processes that contribute to the volume decrease (Figure 3) [6,19,21,22]. These preclinical findings indicate that the hippocampal volume loss observed in depressed patients is due to impaired neuroplasticity and cellular resilience. Most of this is probably reversible and not a result of neurodegenerative processes.

IV Structural plasticity beyond the hippocampus

Major depression is a complex disorder that affects many brain structures, often to a varying extent. Brain changes associated with major depression have been reported for the hippocampus, amygdala, caudate nucleus, putamen, and frontal cortex, structures that are all extensively interconnected (Figure 4). They comprise a neuroanatomical circuit termed the limbic–cortical–striatal–pallidal–thalamic tract. In view of this, the hippocampal changes have to be seen in a broader context, since it is unlikely that disturbed neurogenesis and structural changes in the hippocampus alone will fully explain a disorder as complex as major depression.

The amygdala, as a crucial structure in emotional regulation and formation of emotional memories, evidently plays an essential role in the pathophysiology of mood disorders. In depressed patients, functional neuroimaging studies have identified abnormalities of resting blood flow and glucose metabolism in the amygdala and in the orbital and medial prefrontal cortical areas that are extensively connected with the amygdala [23]. A morphometric analysis using MRI revealed that depressed women had a smaller amygdala core, while another study of men and women reported on a larger total amygdala volume in depressed subjects [24,25]. In addition, post mortem histopathological studies revealed a reduced number of glial cells in the amygdala in major depressive disorder, while no change was found in neuron numbers [26].

The prefrontal cortex (PFC) has strong reciprocal connections with the hippocampus, and dysfunction of the PFC is hypothesized to play an important role in the etiology of major depression. Post-mortem studies in humans revealed reduced neuronal densities, smaller neuronal somata, and a significant decrease in cortical thickness [27,28]. Although the underlying processes for these prominent reductions have yet to be elucidated, a possible and indirect explanation comes from studies in rats showing corticosterone and stress-induced dendritic reorganization in pyramidal neurons, particularly in the medial PFC. These findings suggest that similar neurochemical mechanisms could mediate the dendritic alterations seen in the hippocampus and PFC as a result of stress exposure or high levels of glucocorticoids. Interestingly, antidepressants such as tianeptine and, to a lesser extent, fluoxetine were able to reverse long-lasting inhibition of long-term potentiation, also in the PFC [29].

The demonstration that various antidepressant treatment strategies can stimulate neurogenesis in the adult dentate gyrus, a region of hippocampal formation, has been followed by studies showing similar stimulatory effects on cell proliferation and gliogenesis in the medial PFC of rats. Moreover, it was demonstrated that chronic stress inhibits cell proliferation and gliogenesis not only in the hippocampus, but also in the medial PFC of the animals, and that this inhibitory effect of stress can be counteracted by treatment with the selective serotonin reuptake inhibitor fluoxetine [30]. These findings gain emphasis in light of the fact that in vivo neuroimaging studies in patients

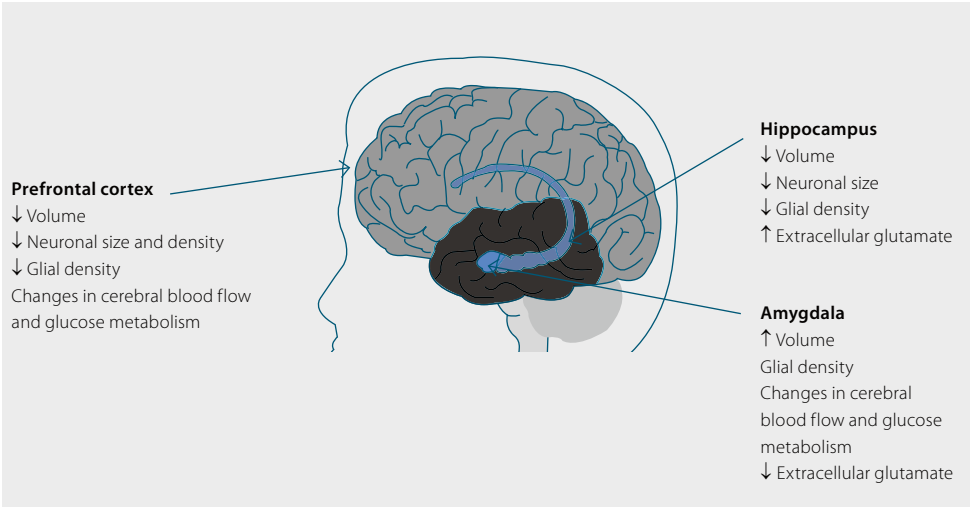

Figure 4. Structural and functional changes as a consequence of stress and / or major depression in hippocampus, amygdala and prefrontal cortex.

with mood disorders have most consistently pointed to the involvement of prefrontocortical sites in the pathophysiology of the disease. The imaging findings are supported by reports on human post-mortem material from patients with mood disorders revealing not only that neurons are affected but also that the number of glial cells is changed in the same prefrontal areas [28].

V Structural plasticity of glutamatergic axons

It has been repeatedly shown that chronic stress changes dendrites and spines and modulates the expression of synaptic molecules. These processes all may impair information transfer between neurons. However, in a recent study, it was shown that expression of M6a, a glycoprotein that is localized in the axonal plasma membrane of glutamatergic neurons, is differentially affected by stress in a region-dependent manner [31]. The expression of the M6a gene had been shown previously to be regulated by chronic social stress [32]. A detailed analysis revealed that only the splice variant M6a-Ib, which is strongly expressed in the brain, is significantly affected by chronic stress in male rats [31]. Quantitative in situ hybridization demonstrated that M6a-Ib mRNA in dentate gyrus granule neurons and in CA3 pyramidal

neurons is downregulated, whereas M6a-Ib mRNA in the medial prefrontal cortex is upregulated by chronic stress. This is the first study showing that expression of an axonal membrane molecule is differentially affected by stress in a site-specific manner. One may speculate that diminished expression of the glycoprotein leads to reduced axonal output of hippocampal neurons. Enhanced M6a-Ib expression in the medial prefrontal cortex might be interpreted as a compensatory mechanism in response to changes in axonal input from the hippocampus. These findings provide evidence that in addition to altering dendrites and spines, chronic stress also changes the integrity of axons and may thus impair information transfer even between distant brain regions.

VI The impact of glia

The most abundant cells within the central nervous system are the glia cells. In the adult brain, there are 10 to 50 times more glia cells than neurons. Classically, three different types of glia cells can be distinguished: astrocytes, oligodendrocytes, and microglia. Astrocytes are the most abundant type of glial cells, accounting for about one-third of brain mass. These cells provide a structural framework for the brain, maintain pH and ion homeostasis in the extracellular space, supply energy and nutrients to the neurons, clear neuronal waste, and, through their end feet on blood vessels, are involved in monitoring of peripheral changes in blood composition. Furthermore, recent studies revealed that besides these "housekeeping" functions, astrocytes are dynamic regulators of synaptic strength, synaptogenesis and neuronal production in, for example, the adult dentate gyrus. Astrocytes also possess receptors for neurotransmitters and steroid hormones that, in a similar manner to receptors in neurons, can trigger electrical and biochemical events in the astrocyte.

During recent years, abnormalities in glial functions have been shown to contribute to the impairments of structural plasticity and overall pathophysiology of mood disorders [33,34]. Reductions in glial number appear to be common in limbic and extralimbic structures such as the amygdala and the prefrontal, orbitofrontal and cingulate cortices of depressed patients. Despite the growing recognition of the importance of glial cells in neurophysiological and neuropathological conditions, relatively little attention has been paid

so far to possible numerical or morphological changes in glial cells, or to alterations in gliogenesis in psychiatric diseases.

As revealed in preclinical studies in animal models of stress, antidepressant treatments can induce changes in gliogenesis, glial morphology and cell number. For example, reduced gliogenesis has been reported in the adult rat hippocampus after glucocorticoid treatment, and electroconvulsive seizure treatment could reverse this effect. In a chronic social stress model of depression, the number of astrocytes (as revealed by immunoreactivity for the glial fibrillary acidic protein) in the hippocampus was significantly reduced, but concomitant treatment with fluoxetine could block this stress effect [35]. Furthermore, in the same experimental paradigm, both stress and drug treatment altered the somal volume of the astrocytes, which might be one explanation for hippocampal volume changes.

One example for neuron–glia communication and dendritic remodeling within the hippocampus involves the glial glutamate transporter GLT-1, which is the predominant glutamate transporter in the rat hippocampus. Exposure to chronic restraint stress increased GLT-1 mRNA and protein expression in the dentate gyrus and CA3 regions of the rat hippocampus [36], an effect that is notably inhibited by the antidepressant tianeptine. Interestingly, tianeptine also

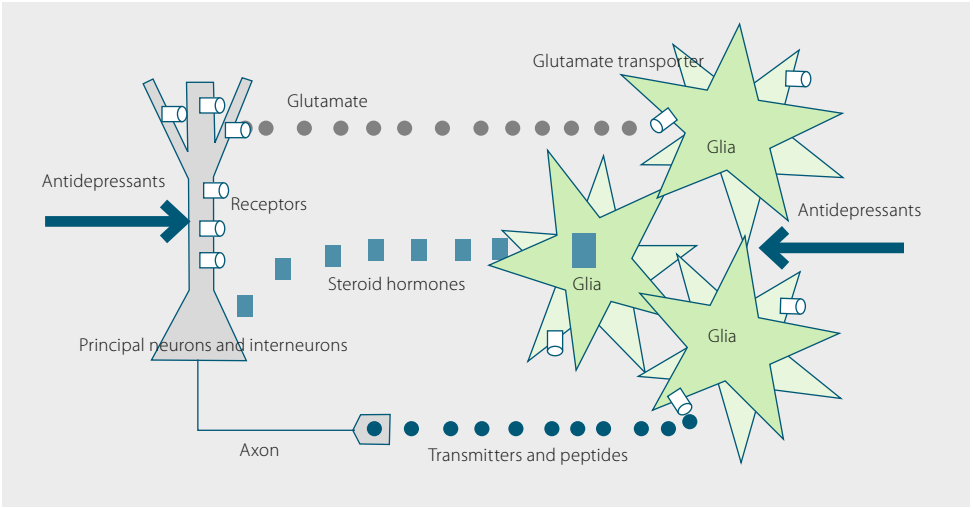

Figure 5. The neuroplasticity hypothesis of the pathophysiology of stress and major depression. Antidepressants act on the neuronal and glial level to correct impairments of structural plasticity and cellular resilience.

inhibits and even reverses stress-induced dendritic remodeling of CA3 pyramidal neurons [12]. Therefore, the modulation of glial GLT-1 expression in CA3 can be considered a subregion-specific neurochemical correlate of dendritic remodeling, a further possible factor explaining hippocampal volume changes.

VII Conclusions

During the last five decades our view of mood disorders and the action of antidepressants has changed significantly. Starting with the idea of a chemical imbalance in the brain, our view has extended toward the neuroplasticity hypothesis (Figure 5). A current view is that effective antidepressant treatments should act by restoring structural as well as functional alterations in neural circuits and, as a fundamental principle, should support the processes of adaptive neural plasticity that underlie normal brain functioning. From current clinical and preclinical studies, it is not yet possible to decide whether a failure of structural plasticity is the cause or the result of neuropathological processes that manifest themselves as depressive symptoms, or whether a failure of neuroplasticity just correlates with depression. Answers to these questions are crucial in order to fully understand the etiology and pathophysiology of disorders as important and clinically relevant as major depression.

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GLUTAMATE-MEDIATED NEUROPLASTICITY DEFICITS IN MOOD DISORDERS

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I Introduction

The resiliency of an organism depends upon its ability to adapt to stressful events or circumstances. The cognitive and behavioral components of resiliency require neuronal adaptations involving a number of brain regions and neurotransmitter systems. Neuroplasticity is a broad term referring to a collection of events critical for neuronal adaptation, including those that occur at the molecular, cellular and systemic levels. While a number of different signaling molecules contribute to neuroplasticity-related changes in neural function, most forms of neuroplasticity require the involvement of glutamate, the primary fast-acting excitatory neurotransmitter in the mammalian brain. Substantial evidence suggests an important role for glutamate in long-term potentiation (LTP), regulation of spine density, and synaptic reorganization, events thought to impact an organism's overall behavior and adaptive potential. Indeed, it has been suggested that altered or impaired neuroplasticity may contribute to a variety of pathological states associated with dysregulation of mood [1]. Thus, the goal of this chapter is to focus on glutamate's role in neuroplasticity in brain structures associated with regulation of mood and emotional behaviors, with particular emphasis on psychiatric illnesses such as major depressive disorder.

II The glutamatergic system

Glutamate is the primary excitatory neurotransmitter in the mammalian brain [2]. De novo synthesis of glutamate arises predominantly from either glutamine or glucose metabolites, although recycling of glutamate from the synaptic cleft via high-affinity neuronal and astrocytic glutamate transporters also occurs. Studies also indicate that glutamate–cystine exchangers may play an important role in glutamate availability [3]. Thus, glutamate synthesis and availability are tightly regulated by both neuronal and non-neuronal mechanisms.

It is well established that multiple metabotropic and ionotropic receptors are involved in mediating the effects of glutamate [2]. Three main types of ionotropic receptors exist, including amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA) receptors. The ionotropic receptors are critical mediators of fast excitatory transmission, and therefore are involved in a wide variety of functions. The metabotropic glutamate receptor (mGluR) family consists of eight members, mGlu1R–mGluR8. Structurally, members of the mGluR family display a seven transmembrane domain structure similar to that observed in other G-protein-coupled receptors [4]. The mGluR family is widely distributed throughout the CNS and can be located either pre- and postsynaptically, as well as extrasynaptically, making these receptors an attractive therapeutic target for a variety of pathologies [5].

III Glutamatergic projections and anatomical substrates of mood-related disorders

Psychiatric disorders such as major depressive illness are tremendously heterogeneous in terms of etiology and manifestation. Thus, they certainly reflect dysfunction of numerous brain regions and circuits. Nonetheless, several structures that serve as key "nodes" in cortico–limbic circuitry have received greater attention due to their consistent apparent involvement in several aspects of these disorders. One example is the prefrontal cortex (PFC), a frontal lobe structure critical for executive functions and motivational behavior [6]. The PFC is highly interconnected to both cortical and subcortical structures, allowing it to modulate cognition, as well as limbic activity [7]. Recent evidence suggests that in certain depressive illness patients, the degree to which executive functions are impaired predicts the outcome of antidepressant efficacy (greater impairment equals poorer efficacy) [8]. Additionally, one of the most consistent findings associated with depressed individuals is alterations in PFC volume [9].

Similarly, recent evidence suggests that posttraumatic stress disorder (PTSD) patients display altered PFC activity during associative learning and memory [10], as well as during processing of fearful stimuli [11]. Individuals diagnosed with other anxiety disorders such as blood-injection-injury phobia also display decreased activation of the medial PFC during presentation of

phobia-relevant stimuli [12]. This finding is congruent with data suggesting that cerebral blood flow is reduced in the PFC during presentation of anxiety-provoking cues in individuals suffering from simple animal phobias [13]. Therefore, evidence continues to suggest that the PFC plays an integral role in the etiology of several psychiatric illnesses.

Another structure that has gained considerable attention over the past decade is the amygdala, a key limbic loop structure located in the temporal lobe of the brain [14]. The amygdala receives excitatory glutamatergic inputs from multiple sources, including thalamic and cortical regions, and also sends glutamatergic projections to various target sites [15]. These glutamatergic afferents are critical for relaying "affective significance of sensory events", and in general are essential for the acquisition and expression of conditioned fear behaviors [16]. Evidence suggests that depressive illness patients have impaired functioning in emotional tasks involving the amygdala [17], while others have reported a positive correlation between amygdalar metabolism and negative affect in depressed individuals [18]. There is inconsistency in the evidence regarding whether or not depressed individuals show structural changes in the amygdala, and in cases where structural changes are observed, directionality is not always consistent [7]. These disparities may be related to differences in methodology, illness duration, patient history, sex, age, and sample size, and therefore suggest that the amygdala may exhibit time- and treatment-dependent changes. If true, then it is possible that the amygdala may be an important initiation site for (or contributor to) structural changes observed in other brain regions of depressive illness patients. Another complicating factor is the anatomical heterogeneity of the amygdalar complex, since human imaging studies generally lack the spatial resolution required to document subregion-specific alterations in amygdalar volume.

Heightened amygdalar activity has also been described in PTSD patients during processing of fearful stimuli [11], although some studies indicate that amygdalar activation in individuals with social phobia is decreased during presentation of anxiety-provoking mental imagery [19]. Still others report that individuals with social anxiety disorders display enhanced amygdala activation during processing of emotionally relevant stimuli [20]. Collectively, the amygdala appears to be a critical player in both depressive illness and anxiety-related disorders.

A final structure that has received much attention is the hippocampus, a limbic structure also critical for regulating emotional behaviors as well as cognitive processes [1]. The hippocampus has reciprocal glutamatergic connections with a number of cortical and subcortical structures, including the amygdala [21] and PFC [22]. Deficits in hippocampus-dependent cognitive tasks have been described in subsets of depressive illness patients [1], and, interestingly, marked reductions in hippocampus volume are consistently found in a variety of depressive illness patients. There has also been speculation that hippocampus deficits may underlie some of the feelings of worthlessness, hopelessness, guilt, doom, and suicidality that accompany depression [23].

Recent evidence demonstrates that PTSD patients display altered hippocampus activity during associative learning and memory [10], whereas individuals diagnosed with social anxiety disorder display decreased activation of the hippocampus during mental imagery of an "anxiogenic social situation" [19]. Decreased cerebral blood flow to the hippocampus has also been noted in individuals diagnosed with small animal phobias during presentation of phobia-relevant stimuli [13]. Thus, abnormalities in the hippocampus appear to be associated with a variety of disease states, and therefore further investigation of whether alterations in this structure serve as cause or consequence in psychiatric illness will provide greater insight regarding the anatomical substrates of mood-related disorders.

IV Glutamatergic alterations in psychiatric illness: clinical evidence

Depressive illness

Alterations in central glutamatergic transmission have been described in a variety of types of depression. For example, some studies indicate that increased glutamate levels are present in brain structures of depressed individuals [2], whereas examination of other structures such as the anterior cingulate gyrus indicate that glutamine-to-glutamate ratio (Glx) is decreased [24]. This finding is echoed by reports indicating that glutamate levels in the anterior cingulate of subpopulations of pediatric depressive illness patients are also decreased [25]. Of importance is the observation that electroconvulsive therapy can reverse glutamate deficiencies in the anterior cingulate of depressed adults [26], suggesting that glutamate abnormalities in this

region may be critical in the etiology of depression. More recent evidence also suggests that suicidal ideation in depressed individuals is associated with genes that encode ionotropic glutamate receptors [27], whereas others report a positive correlation between plasma glutamate levels and severity of depression [28].

Anxiety disorders

A substantial amount of evidence suggests that glutamate may be involved in the pathophysiology of anxiety disorders. For example, recent clinical data indicate that anterior cingulate Glx predicts symptom severity in female obsessive-compulsive disorder patients [29], whereas individuals diagnosed with social anxiety disorder have increased brain glutamate concentrations [30]. In addition to these direct measurements, circumstantial evidence also exists. For instance, subsets of individuals diagnosed with PTSD display cortical hyperexcitability, a finding supportive of potential alterations in glutamatergic transmission [31]. It has also been reported that use of ketamine, an NMDA glutamate receptor antagonist, increases PTSD symptoms in subsets of patient populations [32]. Lastly, the evidence continues to suggest that glutamatergic drugs are efficacious in treating obsessive-compulsive disorder, PTSD, generalized anxiety disorder, and social phobia [33].

Neuroplasticity deficits in depressive illness
Structure
• Deceased volumes in hippocampus and prefrontal cortex
• Increased/decreased volume in amygdala
• Alteration in neuronal size and density
Functions
• Alterations in cerebral blood flow and metabolism
• Neuropsychological deficits in memory, attention, anxiety
Glutamate neuropharmacology
• Reduced glutamate receptor expression and binding activity
• Reduced glial glutamate transporter activity
• Altered glutamate neurochemical profiles

Table 1. Neuroplasticity deficits in depressive illness.

V Understanding glutamate's involvement in neuroplasticity: functional implications in relation to psychiatric illness

Clinical studies are limited in their ability to identify the underlying electrophysiological, neuroanatomical and neuropharmacological deficits that ultimately contribute to psychiatric illness. However, it is plausible that glutamatergic alterations may promote dysregulated neuroplasticity and subsequent manifestation of psychiatric illness (see Table 1). For these reasons, preclinical investigations have relied upon experimental models, including chronic stress paradigms, for the study of psychiatric diseases such as depressive illness. Such studies provide important information regarding

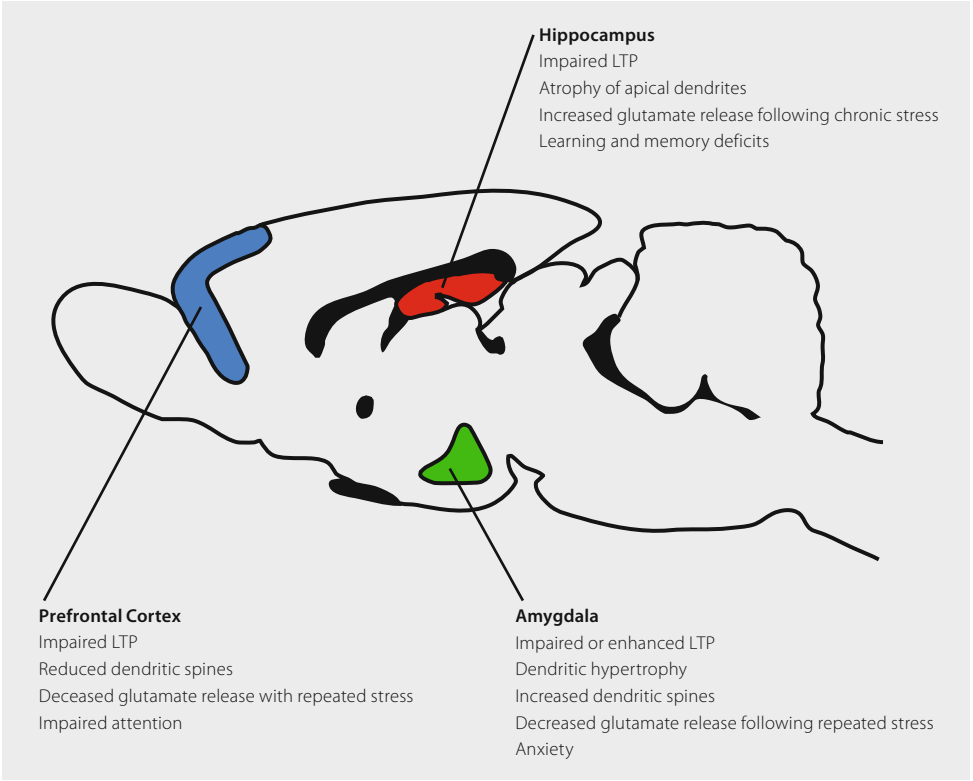

Figure 1. Stress-induced changes in neuroplasticity in animal models: associated glutamatergic and behavioral alterations. In preclinical models of depressive illness, animals subjected to chronic or repeated stress paradigms exhibit deficits in neuroplasticity in the prefrontal cortex (blue), hippocampus (red), or the amygdala (green). This may include electrophysiological deficits such as impairments in long-term potentiation (LTP), neuroanatomical alterations such as changes in dendritic morphology or neuronal spine density and alterations in glutamatergic neurochemical profiles. Ultimately, these structural, neurophysiological and pharmacological changes may contribute to the development of cognitive-behavioral deficits initiated by stress. See text for details.

stress-related effects upon brain plasticity. Indeed, animals subjected to stress exhibit features that are strikingly similar to those observed in depressive patients, including structural and functional alterations in the HC, PFC and amygdala (See Figure 1). Importantly, these preclinical models confirm and extend clinical observations that deficits in the glutamatergic system may be part of the core etiological mechanisms of depressive illness.

Long-term potentiation

LTP is a form of synaptic plasticity thought to represent a cellular correlate of learning and memory [34]. In simple terms, LTP involves the strengthening of synaptic connections as a result of increased activity, a phenomenon utilizing NMDA and AMPA glutamate receptors. Several structures in the CNS exhibit LTP, including the hippocampus, amygdala, thalamus, striatum, cortex and PFC. While LTP in these structures shares many features associated with learning tasks in animals, less is known regarding whether LTP induction results in memory consolidation and concomitant behavioral changes [35]. Yet promising work from the amygdala, a critical structure involved in emotional learning, may provide some of the most compelling evidence linking LTP to learning and memory. For example, LeDoux and colleagues report that fear-conditioning, an amygdala-dependent form of learning, involves LTP-like processes [36], whereas high-frequency stimulation of the thalamo–amygdalar pathway enhances acoustic-mediated evoked field potentials in the amygdala [37]. Furthermore, administration of agents that interfere with LTP impairs acquisition of fear-conditioning in animal models [35]. Collectively, these data strengthen the argument that LTP represents a physiologically relevant model of learning and memory.

The clinical importance of these observations is underscored by data indicating that stress, a well-documented environmental factor associated with a variety of psychiatric diseases such as depression [38], modulates LTP in animal models. For example, acute stress has been shown to impair hippocampus [39] and PFC LTP [40;41], whereas in the amygdala acute stress can either impair [42] or enhance LTP [43]. Repeated or chronic stress, conditions capable of producing depressive-like states in animal models [44], impair hippocampus [43] and PFC LTP [45], but not amygdalar LTP [43]. Moreover, it has been proposed that stress-induced modulation of LTP may

contribute to the maintenance of traumatic memories associated with PTSD [31]. Therefore, altered LTP in these structures may account for cognitive and behavioral deficits observed in disease states such as anxiety, depressive illness and/or PTSD [43,46]. Further support for this statement is provided by evidence indicating that agents associated with mood stabilization modulate LTP. Thus, although measuring LTP is not feasible in human populations, the preclinical evidence suggests that altered LTP may serve as a key player in certain psychiatric diseases and that some mood-stabilizing agents may mediate their effects via modulation of LTP-like processes.

Morphological plasticity

Alterations in neuronal morphology, including dendritic length and branching, spine density, and volume, have been widely described in a variety of CNS structures. While the exact mechanisms underlying morphological plasticity are not entirely known, evidence continues to support a role for glutamate. For example, it was originally proposed that increased spine volume in HC dentate gyrus neurons was elicited by glutamate-mediated events [47]. Subsequent studies illustrate that brief exposure of mature HC neurons to glutamate increases the spine cross-sectional area [48], whereas others report an intimate involvement of glutamate transmission in regulation of spine density [49]. More recent evidence suggests that glutamate receptor activation stimulates growth of new postsynaptic processes in HC neurons [50].

Mechanistically, it is believed that activation of both NMDA and AMPA glutamate receptors contributes to these types of morphological plasticity [48]. However, it is important to note that excessive glutamate receptor modulation has been associated with destabilization of synaptic structure [51], as well as loss of axonal neurofilament proteins [52]. Therefore, further studies are necessary to more thoroughly explore the conditions which dictate the dualistic role of glutamate in morphological plasticity.

The functional significance of morphological plasticity can be viewed on a very simplistic level as having importance for defining intrinsic membrane properties of, as well as communication between, neurons [53]. Yet, morphological changes in adult rat brain structures occur readily under pathologically relevant conditions. For example, increased dendritic branching in the

basolateral complex of the amygdala is observed following 10 days of immobilization stress, an event associated with enhanced amygdala-dependent behaviors [54]. Conversely, atrophy of hippocampus apical dendrites occurs following 21 days of chronic restraint stress, a phenomenon associated with spatial learning and memory deficits. Morphological changes also reportedly occur in the PFC following 21 days of chronic stress and are associated with impaired attention-selection processes [55]. Other animal models of PTSD [56] and depression [57] also display morphological abnormalities in various brain structures.

Importantly, stress-associated alterations in morphological plasticity in animal models can be mitigated or blocked by agents associated with mood stabilization [54]. Perhaps restoration or normalization of glutamatergic tone underlies this phenomenon. For example, pharmacological manipulation of the glutamatergic system mitigates stress-induced morphological changes in the hippocampus of animal models [1,54,58], whereas the antidepressant tianeptine, a modulator of glutamatergic transmission, inhibits stress-induced morphological changes in both the hippocampus and amygdala [54]. Indeed, our most recent evidence suggests that tianeptine "normalizes" glutamate efflux in the central amygdala (CeA) of rats subjected to repeated stress, whereas a similar phenomenon also takes place in the hippocampus of animals subjected to chronic stress (Figure 2). Lastly, clinical data suggest that structural abnormalities in a number of brain regions are present in numerous disease states. For example, abnormalities in amygdalar volume have been described in subpopulations of depressive illness patients [7], as well as individuals with PTSD [59]. Similarly, the hippocampus displays structural abnormalities in subsets of individuals diagnosed with major depressive disorder [60] and PTSD [61], whereas structural alterations in the PFC have been described in populations of patients diagnosed with bipolar disorder [62] and PTSD [63].

Treatment implications

A substantial amount of literature suggests that glutamate homeostasis may be an important therapeutic target for several disease states. Indeed, pharmacological alteration of glutamatergic transmission produces anxiolytic effects in a variety of amygdala-dependent behaviors, including in

the fear-potentiated startle and elevated plus maze tests [33]. It has also been reported that clonidine administration in male rats alleviates memory impairments by correcting hippocampus glutamate hypofunction [64]. As stated above, we recently demonstrated that administration of the antidepressant tianeptine normalizes stress-mediated glutamate release in the rat amygdala, a finding that can be interpreted to indicate that a potential mechanism of some mood-stabilizing drugs may include modulation of glutamate release. Indeed, the accumulated data from preclinical studies demonstrate that tianeptine reverses and/or inhibits stress-induced deficits in glutamatergic neuroplasticity in the hippocampus, amygdala, and PFC. These preclinical studies would therefore suggest that tianeptine mediates its clinically relevant effects through normalization of glutamatergic tone, which would restore neuroplasticity in depressive illness patients. These

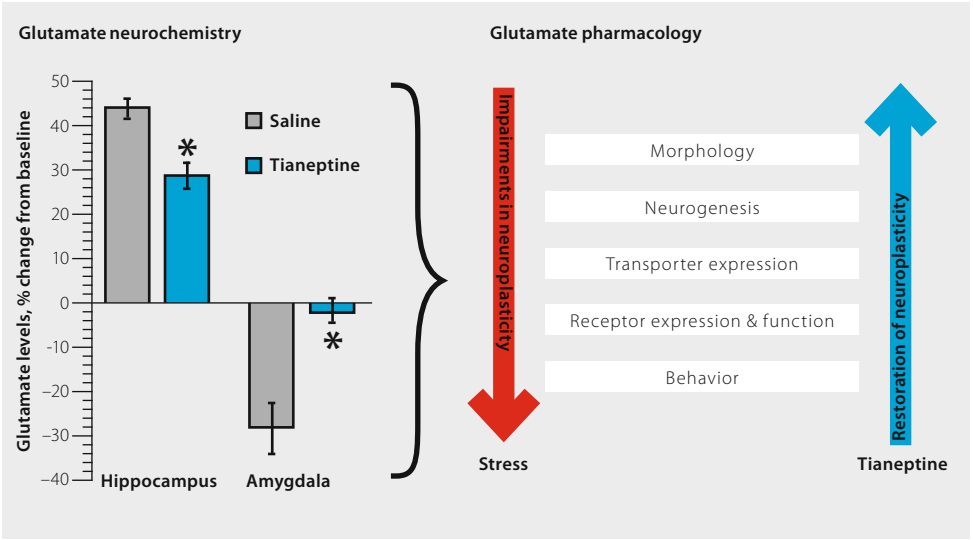

Figure 2. Effects of antidepressant administration on stress-mediated alterations in glutamate efflux in control and repeatedly stressed animals. Stress elicits significant increases in glutamate levels in the hippocampus, but decreases glutamate levels in the amygdala (gray bars). These stress-induced alterations in glutamatergic tone may be an initiating factor for deficits in glutamate pharmacology and physiology in the hippocampus, amygdala and prefrontal cortex that impair neuroplasticity (red arrow). Importantly, stress effects upon glutamatergic neurochemical profiles can be inhibited by the antidepressant tianeptine (blue bars), which provides a potential mechanism through which tianeptine restores stress-mediated deficits in glutamate neuroplasticity in the CNS (blue arrow). Moreover, these results indicate that antidepressants that target the glutamatergic system may provide important and innovative therapeutic interventions in the treatment of mood disorders like major depressive disorder. (Bar graph illustrates changes in glutamate levels in the hippocampus and amygdala in animals given saline [gray] or tianeptine [blue] treatment during an experimental model of depression. Asterisk denotes a significant difference from saline-treated animal.)

novel and innovative mechanisms of action establish tianeptine as a pioneer in new treatment strategies for patients with mood disorders. Interestingly, growing clinical evidence also suggests that agents associated with modulation of glutamate transmission may be efficacious in the treatment of several types of psychiatric illnesses. For example, lamotrigine [65] and riluzole [66], compounds that reduce glutamate transmission, are effective in subsets of patients diagnosed with depressive illness. Subchronic administration of lithium in healthy volunteers has also been reported to reduce glutamate transmission in some CNS structures [67], whereas use of mGluR agonist LY354740 reduces fear-potentiated startle in humans [68].

VI Conclusions

Significant progress has been made in discerning the neurochemical and neuroanatomical correlates of many psychiatric diseases. Out of these efforts a growing appreciation of the role of glutamate and neuroplasticity has evolved. Considering the temporal disparity between the neurochemical response to psychiatric drug treatment (which occurs on a timescale of minutes to hours) and the therapeutic response (which typically occurs within weeks), it is interesting to postulate that glutamate may serve as a key neurochemical mediator linking these distinct phenomena. Thus, although additional studies are necessary to define this relationship more thoroughly, the evidence to date suggests that glutamate transmission in the CNS, with its widespread distribution and rich variety of receptor subtypes and regulatory elements, possesses key clinical significance as a promising novel therapeutic target.

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REGULATION OF CELLULAR PLASTICITY IN MOOD DISORDERS: THE ROLE OF THE AMPA RECEPTOR

Per Svenningsson and Bruce S. McEwen

I Introduction

The pathophysiology of mood disorders has been an area of research for many years, but the precise neurobiological mechanisms that underpin these common conditions remain unclear. For much of the second half of the 20th century, the principal focus was on the role of monoamine neurotransmitters (in particular noradrenaline and serotonin, as well as dopamine) and their receptors, which are prominent in the limbic regions and prefrontal cortical areas that are known to be involved in many of the manifestations – both affective and physiological – of mood disorders. This focus has yielded an improved understanding of the neural mechanisms involved in mood disorders; moreover, it has led to the development of several major classes of antidepressant agents (notably the monoamine oxidase inhibitors, the tricylics, and the selective serotonin reuptake inhibitors [SSRIs]), all of which block either the oxidation of monoamines or their reuptake by neurons [1]. Nevertheless, various observations arising out of successful therapeutic approaches to depression have also led to an appreciation that pathophysiological explanations of depression do not lie solely, or even mainly, with the monoaminergic system [2,3]:

- increased monoamine receptor selectivity does not necessarily yield increased efficacy;
- a simple role for monoamine neurotransmitters does not successfully explain the delay in clinical effect (sometimes of several weeks) that is routinely seen with antidepressants;
- electroconvulsive therapy, a non-drug treatment that does not apparently affect the monoamine systems, is efficacious;
- not all drugs that increase monoamine levels are effective anti-depressants;
- some effective antidepressants have only very weak effects on the monoamine transmitter system; and
- other effective antidepressants (such as tianeptine) are glutamatergic system modulators rather than inhibitors of monoamine reuptake, a

somewhat paradoxical finding and one that is in contrast to the primary action of the tricyclics and the SSRIs.

The realization that the monoaminergic neurotransmitter system does not hold the complete answer, despite the proven efficacy of many antidepressants that affect this system, has prompted exploration of other possible neural mechanisms that may underlie the pathophysiology of depression. One of these involves the glutamatergic system and its role in neuroplasticity. This chapter looks briefly at ways in which the regulation of the glutamatergic system may play a role in mood disorders and their treatment, and it examines findings from a recent study assessing the effects of tianeptine, a novel antidepressant, on glutamate receptors [4] – findings that suggest that phosphorylation of glutamate receptors is important in the pathophysiology of depression and that may point, in turn, the way to the exploration of new therapeutic approaches.

II Neuroplasticity, glutamate, and glutamate receptors

Multiple neuronal circuits appear to be involved in the neuropathology of mood disorders, which is consistent with the complex and wide-ranging clinical features seen in patients with these conditions. Evidence is accumulating that depression is associated with impaired neuroplasticity, manifesting itself in part as reduced numbers of glial cells and alterations in the size and density of cortical neurons in the frontal–limbic areas [5,6]. Studies have repeatedly reported atrophy within the hippocampus in depressed subjects [7,8], and moreover this atrophy appears to be related to the severity and duration of the depression [8,9]. Significantly, treatment with certain antidepressants has been shown to correct some of these dysfunctions, although the mechanisms remain unclear [10–13].

Glutamate is the principal excitatory synaptic neurotransmitter and it is key to such attributes as learning and memory – attributes that are dependent on neuroplasticity. Glutamate is also increasingly being suggested as a major neurotransmitter in many of the behavioral and physiological features that characterize mood disorders, including cognitive functioning, learning, and memory.

Glutamate does not cross the blood–brain barrier and it is therefore produced within the central nervous system, primarily from glucose metabolism

mediated by enzymes contained both in neurons and in glial cells [14]. Once glutamate is released from neurons its extracellular concentration is tightly regulated, principally by a sodium-dependent reuptake mechanism that utilizes a series of glutamate transporter proteins. Although the mechanisms by which glutamate levels in the extracellular space are regulated are not completely known, it is thought that phosphorylation of the transporter proteins by protein kinases is involved in controlling the activity of the transporters and therefore the glutamate concentration. In addition, glutamate levels are known to rise rapidly and to excitotoxic levels in response to stress or trauma or ischemic injury, probably as a result of impaired transporter function [15,16].

III Glutamate receptors

Two broad types of glutamate neuronal receptors have been identified: the ionotropic receptors and the metabotropic receptors. Ionotropic glutamate receptors are generally located post-synaptically and mediate fast excitations and synaptic plasticity by means of gated sodium and calcium ion channels. Metabotropic glutamate receptors are more widely distributed, act mainly via G-protein-coupled signaling cascades and serve to modulate post-synaptic glutamatergic excitation by means of positive or negative feedback to glutamate release [14,17].

Ionotropic glutamate receptors comprise the *N*-methyl-D-aspartate (NMDA) receptors, the alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, and the kainate receptors. In the adult brain, NMDA and AMPA receptors are found in high concentrations in the cerebral cortex, hippocampus, striatum, septum, and amygdala [18], and they are found together in about 70% of synapses [19]. In contrast, however, at birth and in early life, most of the excitatory synapses in these areas contain NMDA receptors but not AMPA receptors; the concentration of AMPA receptors increases during the course of post-natal brain development until the co-localization that is characteristic of the mature brain is achieved. This increase in synaptic AMPA receptors is a regulated process that depends in part on activation of NMDA receptors, and it is an important aspect of some forms of neuroplasticity at synapses, both in the developing brain and in the mature brain.

IV NMDA receptors and their interaction with AMPA receptors

NMDA receptors are activated by glutamate, but this activation also requires depolarization of the post-synaptic membrane because, at membrane potential, the NMDA ion channel is blocked by magnesium ions. Membrane depolarization is mediated by the activation of another post-synaptic receptor (e.g. an AMPA receptor) at the same synapse, and this depolarization removes the magnesium blockade and permits the NMDA receptor to open and allow the entry of sodium and calcium ions [17]. NMDA receptors are composed of NR1 and NR2A-D subunits. The functional properties of NMDA receptors are also determined by the type of NR2 subunit they contain.

Both the NMDA receptor and the AMPA receptor are important in the regulation of synapse neuroplasticity [20], the best studied forms of which are long-term potentiation (LTP) of synaptic neurotransmission, a phenomenon that refers to strengthening of synaptic contacts by repeated stimulation, and, conversely, their long-term depression (LTD). The influx of calcium caused by glutamatergic activation of the NMDA receptor sets off a cascade of signals, one result of which is the formation of complexes between calmodulin-dependent protein kinase II (CaMK-II) and the NMDA receptors themselves. These complexes promote phosphorylation of both the enzyme and the complex. This phosphorylation is thought to represent a "memory switch" [21], leading to multiple changes at the synapse. For example, the CaMK-II–NMDA receptor complex probably produces new anchoring sites at the synapse for AMPA receptors, and – importantly for this discussion – glutamate-activated AMPA receptors are themselves phosphorylated, which increases their conductance [17].

Moreover, within minutes, the cascade of signals can result in structural alterations to dendrites, seen as changes to the shape and increases in the number of "spines", which mark the site of glutamatergic synapses [22,23]. Such structural alterations may, in time, become permanent.

V AMPA receptors

AMPA receptors occur in various configurations, either homomeric or heteromeric, of four types of glutamate receptor (GluR): GluR1, GluR2, GluR3, and GluR4. Activation of the AMPA receptor requires two molecules of glutamate [17,24].

As noted above, the concentration of AMPA receptors is low in the juvenile brain and increases in a regulated fashion during brain development; this regulation of their concentration continues in adult life. Moreover, AMPA receptors undergo a continual process of endocytosis and exocytosis, and signal cascades are able to alter the synaptic concentration of the receptors in both the long term and the short term [25,26].

It is thought that AMPA receptors are synthesized in the endoplasmic reticulum, deep within the cell body of neurons, and therefore an AMPA receptor must be transported, or trafficked, from the cell body to reach the synapse where it ultimately resides. Egress from the endoplasmic reticulum is a controlled process, whereby GluR1–GluR2 dimers leave the endoplasmic reticulum rapidly and are trafficked to the Golgi complex, whereas GluR2–GluR3 complexes are retained much longer. Some Glu2 subunits are retained apparently indefinitely in the endoplasmic reticulum [27].

The transport of AMPA receptors to the synapse is thought to rely on the system of microtubules in the dendrite, where they are thought to be carried by so-called motor proteins [28,29]. Transport from the microtubular system to the dendritic spines, where most excitatory synapses are found, is accomplished by means of actin filaments, which appear to interact with the GluR1 and GluR4 subunits of the AMPA receptor [27,30].

This AMPA receptor trafficking is thought to provide an activity-dependent regulation of synaptic strength, and it widely accepted that it is an important component of LTP and LTD [17].

VI Effects of stress on glutamate and glutamate receptors

In animal models of uncontrollable stress, extracellular levels of cerebral glutamate, under influence of increased glucocorticoid concentrations, are increased, notably in the hippocampus [31,32]. Glutamate levels can be sufficiently high to cause structural remodeling, leading to reversible structural alterations involving decreased neurogenesis and neuronal shrinkage or growth [1,33]. Blockade of glutamate release or of NMDA receptors prevents this remodeling [6,34,35], as does potentiation of AMPA receptors [36], which implicates glutamate release as a co-modulator along with the actions of glucocorticoids [37]. Under extreme conditions, such as stroke, seizures or

head trauma, excitatory amino acids and elevated glucocorticoids cause neuronal death [38].

VII AMPA receptor phosphorylation and tianeptine

Phosphorylation of the AMPA receptor is now known to play a significant role in their regulation of neurotransmission and plasticity at excitatory synapses [4]. Phosphorylation of at least two sites on the GluR1 subunit is known to upregulate these processes:

- Ser831, phosphorylation of which by protein kinase C (PKC) or CaMK-II augments AMPA receptor currents in the hippocampus [39]; and
- Ser845, phosphorylation of which is required for PKA-mediated potentiation of peak current by the GluR1 receptors [40].

Work over the past few years has strongly suggested that the efficacy of some of the commonly used antidepressant agents may be due in part to their effects on the phosphorylation of AMPA receptors. For example, both the tricyclic imipramine [41] and the SSRI fluoxetine [42] increase phosphorylation at Ser845 on GluR1.

Tianeptine is a glutamatergic system modulator. In animal models of depression, it has been shown to have a number of effects on the glutamatergic neurotransmitter system, including:

- a unique effect in reversing or preventing stress-induced dendritic atrophy in the hippocampus [43,44];
- inhibition of stress-induced changes in glutamatergic neurotransmission [45,46];
- inhibition of stress-induced changes in glutamate receptor expression [47];
- reversal of stress-induced impairment in neurogenesis [48];
- reduction of stress-induced apoptosis in the dentate gyrus of the hippocampus and in the temporal cortex [49]; and
- augmentation of AMPA receptor phosphorylation (see below) [4].

A recent animal study has provided evidence that long-term administration of tianeptine acts to increase phosphorylation at Ser831 on the GluR1 subunit in the frontal cortex and at both Ser831 and Ser845 in the hippocampus, further consolidating our understanding of the role played by changes in AMPA receptor phosphorylation in the pathogenesis of depression. It also highlights the probable importance that augmentation of this phos-

phorylation can have in the pharmacological treatment of depression [4]. Furthermore, this study demonstrated that tianeptine has no binding affinity at monoaminergic receptors or for monoaminergic transporters, thereby strengthening evidence that the action of tianeptine does not depend primarily on its effects on serotonin.

In this study, tianeptine (10 mg/kg) was given to mice, the dose being selected because it has been shown to be sufficient to prevent stress-induced dendritic atrophy [43], to reduce extraneuronal serotonin levels in the hippocampus, and to increase reuptake of serotonin in the cortex and hippocampus [50]. Long-term administration of tianeptine confirmed that the modulation has a significant effect on phosphorylation at these two sites (Figure 1). There was a trend toward increases of phosphorylation at both Ser831- and Ser845-GluR1 following acute administration of tianeptine and, in fact, a more recent study performed in rats showed that even acute adminstration of tianeptine increases phospho-Ser831-GluR1 [51].

VIII Relationships between AMPA receptor phosphorylation and antidepressant effect

These effects of tianeptine were striking. The functional relevance of this finding in terms of any effect of tianeptine on depression was assessed by behavioral analysis of the mice, using two tests that have been shown to be valid animal models for depression: the tail-suspension test [52], which places the animal in an inescapable stress situation, and the open-field test, which assesses locomotion and exploratory behavior. In order to explore the functional importance of Ser831-GluR1 and Ser845-GluR1 in any behavioral effects of tianeptine, GluR1-phosphomutant mice, in which these alleles had been inactivated by replacing these serines with alanines so phosphorylation at these sites of the AMPA receptor could not occur, were studied. Normal (i.e. wild-type) mice and GluR1-phosphomutant mice were given either saline or tianeptine.

In the tail-suspension test, tianeptine increased mobility in the wild-type mice but not in the GluR1-phosphomutant mice. In the open-field test, tianeptine produced a significant increase in exploratory behavior in the wild-type mice but not in the GluR1-phosphomutant mice (Figure 2).

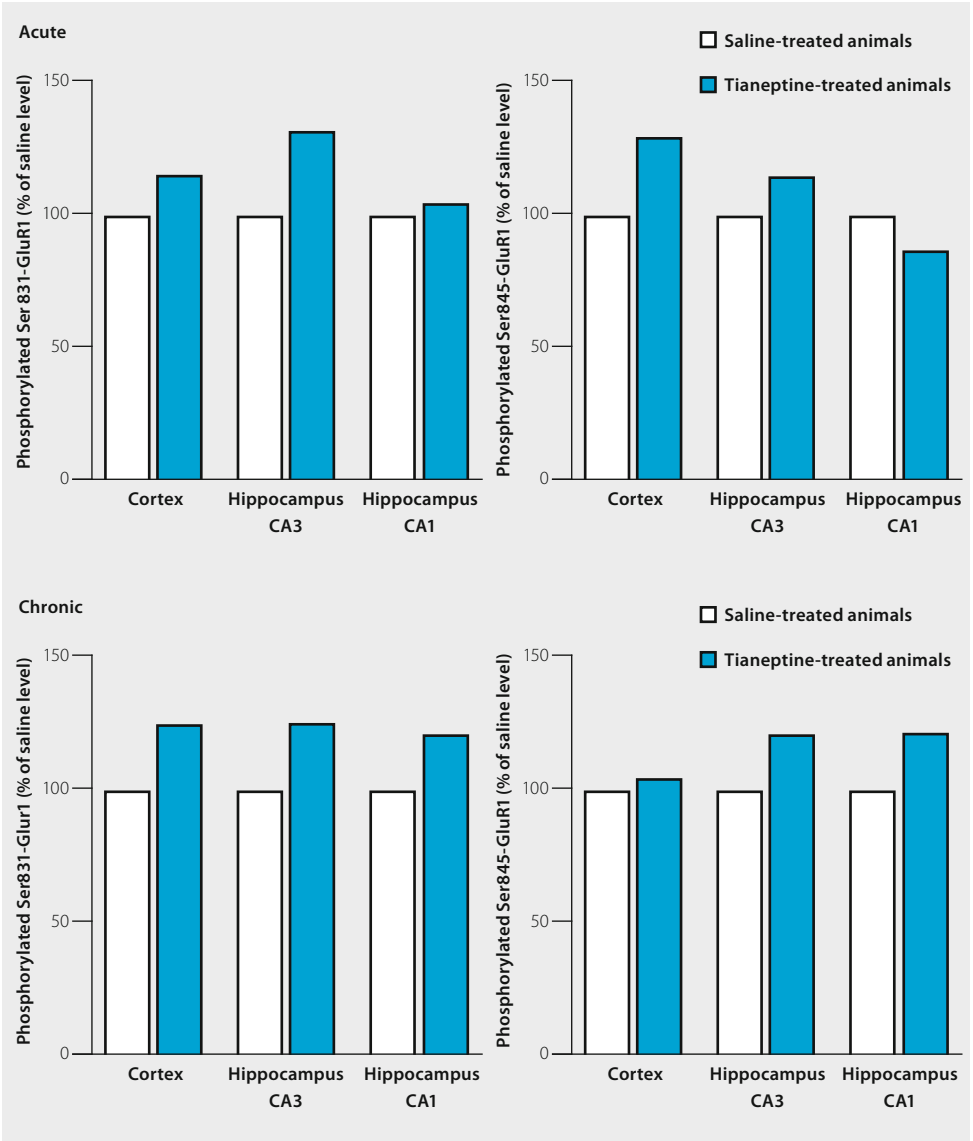

Figure 1. Effect of tianeptine on AMPA receptor phosphorylation in mice. Amounts of phosphorylated Ser831-GluR1 and Ser845-GluR1 were measured in the frontal cortex and in two areas of the hippocampus in mice treated either acutely or chronically with saline or tianeptine. Chronic tianeptine treatment increased Ser831-GluR1 in the frontal cortex and the CA3 region of the hippocampus and Ser845-GluR1 in the CA1 region of the hippocampus. Adapted from Svenningsson et al. [4].

Antidepressants of various classes also promote phosphorylation of other proteins at different sites, including cyclic AMP regulatory element-binding protein (CREB) [11] and CaMK-II [53]. Electroconvulsive shock therapy has also been shown to increase CREB phosphorylation in the hippocampus [54]. In this context, Svenningsson et al. [4] further explored the phosphorylation states of these two proteins in the wild-type mice and the GluR1-phosphomutant mice under baseline conditions. There were higher basal levels of CREB phosphorylation in the frontal cortex in the GluR1-phosphomutant mice than in the wild-type mice. In the hippocampus, CREB phosphorylation in the GluR1-phosphomutant mice was increased in the CA1 region but decreased in the CA3 region compared with the levels in the wild-type mice. Tianeptine altered CREB phosphorylation in the wild-type mice (increasing it in the CA1 region and decreasing it in the CA3 region), but there was no effect of tianeptine in the CA1 region in the GluR1-phosphomutant mice. Interestingly, the effects of tianeptine on the phosphorylation of CREB in the CA3 region of the hippocampus appears to be the opposite of the effects of other antidepressants, and its effects in the CA1 region (in wild-type mice) are more pronounced.

These findings in relation to the effect of tianeptine on CREB phosphorylation in wild-type and GluR1-phosphomutant mice are difficult to interpret directly. They do suggest, however, that the role of the GluR1 protein in the AMPA receptor (and the effect of tianeptine) in the phosphorylation of CREB differs between regions [4], and also that these effects may not be antidepressant per se.

The phosphorylation of CaMK-II did not differ significantly between the wild-type mice and the GluR1-phosphomutant mice, either at baseline or after chronic administration of tianeptine, even though tianeptine increased phosphorylation of GluR1 at its CaMK-II residue, suggesting that the action of tianeptine on the phosphorylation of Ser831 on the GluR1 protein probably involves multiple mechanisms [4].

The effects of tianeptine on c-fos expression in wild-type versus the GluR1-phosphomutant mice revealed further aspects of AMPA receptor involvement. c-Fos is widely used as a functional anatomical marker of biochemical activity [55]; it is increased by the main classes of antidepressant agents and by electroconvulsive shock [56]. In the experiment reported

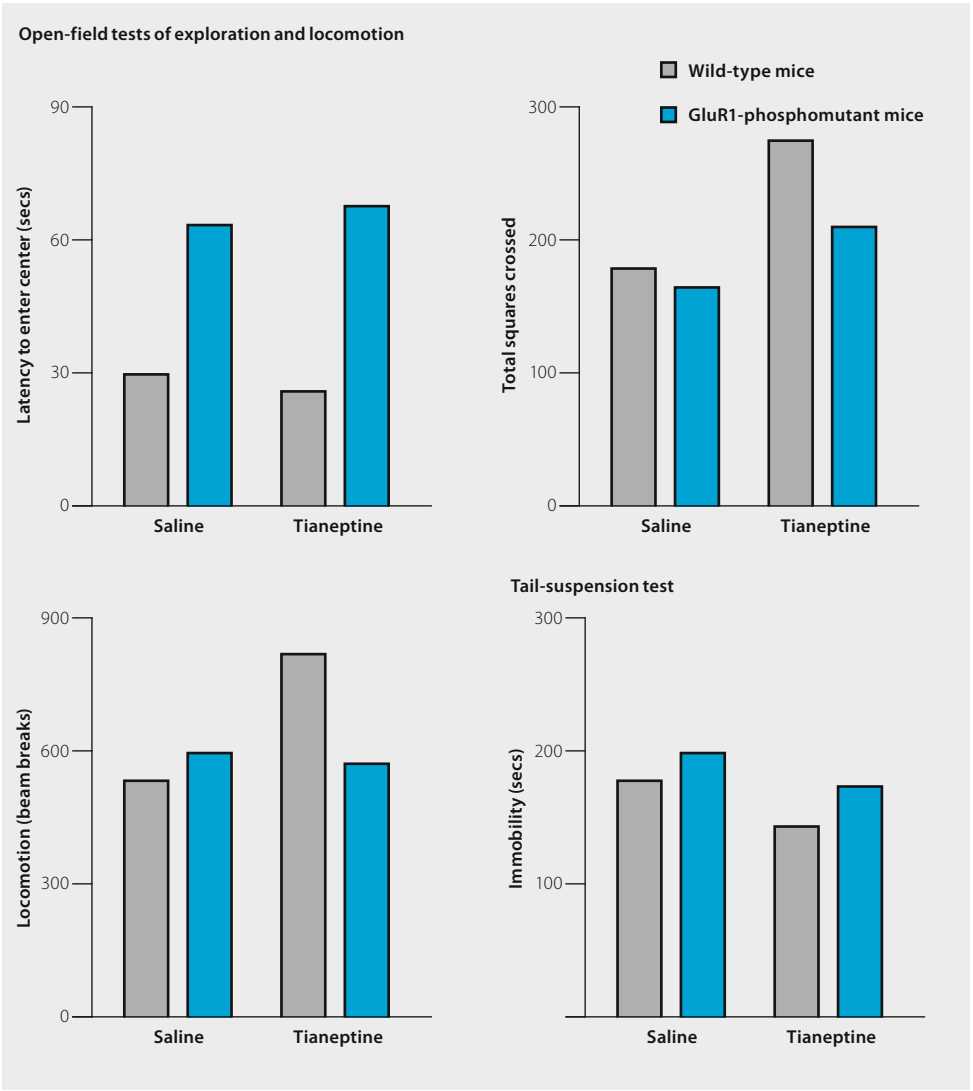

Figure 2. Effect of tianeptine on behavior in mice. Two behavioral parameters (the open-field test, which measures exploration and locomotion, and the tail-suspension test, which is an inescapable stress situation) were assessed in wild-type mice and GluR1 phosphomutant mice after chronic treatment with saline or tianeptine. Saline-treated phosphomutant mice had increased latency to enter the center of an open field and increased immobility in the tail-suspension test. Tianeptine treatment increased open-field locomotion and reduced immobility in the wild-type mice but not in the phosphomutant mice. Adapted from Svenningsson et al. [4].

by Svenningsson et al. [4], saline-treated GluR1-phosphomutant mice had higher c-fos levels in the cingulate cortex than wild-type mice. Tianeptine reversed the higher levels of c-fos found in the GluR1-phosphomutant mice after saline administration but had no effect in wild-type mice. This finding parallels the action of some antidepressants in reversing a stress-induced increase in expression of c-fos [57].

Taken together, these findings indicate the likely importance of AMPA receptor phosphorylation in the pathogenesis of depression and indicate that it may provide a focus of intervention for effective pharmacotherapy, in particular by developing pharmacotherapies, such as tianeptine, that act on this site of action. Indeed, clinical studies have shown that the onset of certain therapeutic actions of tianeptine is more rapid than that of fluoxetine.

IX Conclusions

Depressive illness has been shown to promote structural changes in the central nervous system, particularly in the hippocampus, and to affect glutamate receptor expression and the glutamatergic neurotransmitter system, which is increasingly being recognized as having a key role in the pathophysiology of stress-related depression and in its progression. Increased knowledge of the role of glutamate in depression may point the way to new pharmacotherapeutic modalities.

As discussed above, several of these depression-mediated changes in the glutamatergic system, including changes in AMPA receptor function, have been shown to be inhibited uniquely by tianeptine, and the clinical efficacy of tianeptine may involve unique mechanisms of action that are related to these changes in glutamate receptor expression. Therefore, as well as effectively treating the affective manifestations of depressive disorder, tianeptine may also prevent or reverse certain neurological complications of depression [58].

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CELLULAR PLASTICITY AND THE PATHOPHYSIOLOGY OF DEPRESSION

Thérèse M. Jay

I Introduction

The precise etiology of depression and other mood disorders remains unknown, and causation is likely to be a multifactorial, involving psychological, genetic, social, and biochemical aspects. However, it is becoming increasingly apparent that neuroplastic changes are implicated in the neurobiological mechanisms that underlie depression. Advances in neuroimaging have allowed investigations into the gross anatomical changes in the brain of people with depression; in parallel with this, post-mortem studies of depressed patients and animal studies using models of depression have explored the molecular, chemical, and cellular phenomena that accompany these gross morphological changes.

Such explorations are of clinical importance in that they may point the way to the development of new antidepressant therapies that target the pathophysiology of depression more precisely than currently available treatments, particularly in view of the fact that the neuroplastic changes seen in depression are potentially reversible. One of the chemical changes that is now recognised as important in the underlying pathophysiology of depression is an increase in extracellular levels of the neurotransmitter glutamate; this chapter focuses on the role of glutamate in depression, particularly in the hippocampus and the prefrontal cortex.

II Depression-induced changes in brain morphology and function

The brain is able to adapt itself, both functionally and structurally, in response to stimuli, and it is this plasticity that underlies memory and the ability to learn [1]. Studies of animal models of depression and post-mortem studies of the brains of depressed patients have demonstrated multiple changes in various areas of the brain but particularly in the hippocampus, the amygdala, and the prefrontal cortex.

Hippocampal volume has been shown to be reduced in depression. This change in volume is associated with dendritic atrophy, and a decrease in neurogenesis [2–4].

In the amygdala there is increased dendritic branching in the basolateral nucleus, with reduced neuronal size and decreased density of glial cells. Generally, there appears to be no change in the total volume of the amygdala, but the volume of the core nuclei is reduced. However, in patients with a first episode of depression, the total volume of the amygdala is increased [5–8].

The volume of the prefrontal cortex is reduced; this is associated with reductions in neuronal size and glial cell density. There is reduced brain activity (as assessed by oxygenation levels) [9–11].

These regions are important in mood and emotions and in memory and cognition, and it is thought that these changes mediate some of the characteristic symptoms of depression [12]. The changes are summarized in Table 1.

III Effects of stress and depression on the hippocampus

Stress has been shown to have significant effects on learning and on the ability to lay down new memories. On the one hand, in some circumstances stressful events can enhance learning and memory by altering amygdala-dependent neuronal pathways that influence the hippocampus, striatum, and neocortex [13]. This particularly seems to be so for stress associated with fear [14], and these mechanisms may partly subserve phenomena such as post-traumatic stress disorder [1]. However, stress can also reduce learning ability and impair memory by inhibiting long-term potentiation (LTP) in the hippocampus [15,16].

Studies also suggest that the hippocampus is implicated in the neuropathology of depression. The hippocampus is key to learning and cognition and it controls the hypothalamic–pituitary–adrenal axis, as well as being involved in the neurobiology of anxiety. Studies in humans have demonstrated hippocampal changes associated with depression, often [17, 18] but not always [19] associated with memory impairment, a common feature in depression. All classes of antidepressants that have been analyzed to date have been shown to increase proliferation of new neurons and neuronal survival in the dentate gyrus of the hippocampus, one of the areas of the brain in which – unusually – neurogenesis persists into adult life [20]. The

Neuromorphological changes in animal models of depression and in depressed patients

Animal models

Prefrontal cortex

- Reduction of the number and length of apical dendritic branches in the medial prefrontal cortex
- Reduction in the volume of the upper prefrontal layers of medial prefrontal cortex

Hippocampus

- Dendritic remodeling in CA3 pyramidal neurons, with reversible atrophy shown by shortening and debranching of apical dendrites
- Decreased volume
- Decreased level of N-acetyl aspartate
- Decreased proliferation rate of granule precursor cells
- Decreased adult neurogenesis in the dentate gyrus

Amygdala

- Increased dendritic arborization in spiny pyramidal and stellate neurons

Patients with chronic depression

Prefrontal cortex

- Reduced volume of grey and white matter
- Reduced brain oxygenation
- Reduced neuronal size and reduced density of glial cells

Hippocampus

- Reduced volume (by up to 20%)
- Alterations in blood flow and glucose metabolism

Amygdala

- Volume of core nuclei decreased in chronic depression but total volume retained
- Total volume increased in a first episode of depression
- Alterations in blood flow and glucose metabolism

Orbitofrontal cortex

- Volume reduced

Table 1.
Neuromorphological changes in animal models of depression and in depressed patients. Adapted from Kasper and McEwen [69] and Cerqueira et al. [28].

selective serotonin reuptake inhibitors (SSRIs), the most commonly used class of antidepressants, which act to increase serotonergic neurotransmission, increased hippocampal neuronal proliferation by up to 70% in one rodent study [21], with findings such as this confirmed in subsequent human studies of chronic SSRI treatment [22]. Tianeptine, a glutamatergic system modulator, has been shown to have a similar effect [20] on the hippocampus to that seen with the SSRIs, as have functionally and structurally dissimilar agents such as lithium and valproate [23], and effective non-pharmacological treatments for mood disorders, such as electroconvulsive therapy [24].

Although a direct causal relationship between levels of hippocampal cell proliferation and depression has not been definitively established, these findings from disparate antidepressant therapies lend support to the view that promotion of hippocampal neurogenesis is an important component in their efficacy [24].

IV Beyond the hippocampus: the prefrontal cortex

However, the hippocampus is not the only region that is affected by stress and thereby implicated in the pathogenesis of depression. Most studies performed today on the effects of stress use the hippocampus as only one brain region that could be influenced by stress and involved in corticosteroid actions, and chronic stress is known to cause profound behavioral changes in humans and in rodents, changes that can be best explained by changes in cortical neurological function.

Indeed, significant modifications of metabolism and cerebral blood flow have been found in precise regions of the prefrontal cortex (principally the anterior cingulate cortex), regions that are directly connected to the hippocampus, the amygdala, and other areas of the prefrontal cortex. A working model of depression based on a limbic–cortical dysregulation was proposed by Mayberg in 1997 [25]. According to this model, a depressive episode could be considered as the net result of maladaptive interactions among a set of limbic–cortical regions that are normally responsible for maintaining homeostatic emotional control in response to cognitive and somatic stress. Consistent with this model, not all stress-induced dysfunctions can be explained by hippocampal injury; the deficits in executive function that characterize stress-related disorders is an example.

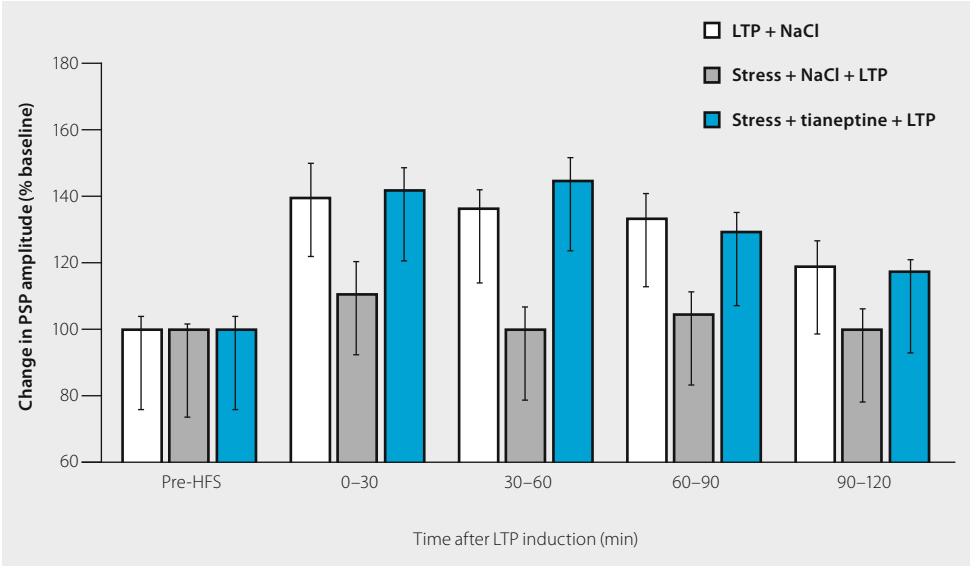

Figure 1. Long-lasting impairment of hippocampal–prefrontal long-term potentiation (LTP) in rats previously exposed to an acute behavioral stress and reversal by an antidepressant tianeptine (dose: 10 mg/kg) [27]. HFS, high-frequency stimulation; PSP, postsynaptic potential.

Study data have now extended the impact of stress to cortical and subcortical brain structures other than the hippocampus (Figure 1) [26]. Acute and chronic stress has been shown to impair synaptic plasticity in the prefrontal cortex by reducing long-term potentiation in the hippocampal–prefrontal connection (Figure 1) [27,28], with a severe disruption of working memory and behavioral flexibility when rats were exposed to stress for a longer period [28]. Other studies [29–32] have showed that chronic stressors or glucocorticoids produce profound rearrangements of the apical dendrites of layer II–III pyramidal neurons in the prefrontal cortex, resulting in atrophy of the distal dendritic branches and loss of dendritic spines.

These findings provide evidence for a fundamental role of the prefrontal cortex in maladaptive responses to stress and identify this area as a target for intervention in stress-related disorders [33].

V Animal models of depression

Animal models are useful for studying chemical and histopathological changes that accompany disease. However, it is acknowledged that it is difficult to develop a true animal model of depression and other psychiatric

disorders since mental illnesses are probably a uniquely human condition and, in any case, typical symptoms of depression cannot be modeled in animals [34]. Nevertheless, there is a strong causal relationship between stressful life events and depression in humans; moreover, there is striking similarity between the physiological, endocrinological, and neuromorphological changes seen in animals subjected to stress and those seen in depressed patients [35]. Animal models of psychiatric disorders should fulfil three major criteria [20]:

- face validity – the degree to which the symptoms seen in the animals resemble those seen in humans;
- predictive validity – the degree to which the animals respond favorably to the same drugs as humans do; and
- construct validity – the degree to which the animal model is consistent with the theoretical rationale.

Researchers have developed a number of animal models using such paradigms as prenatal stress, maternal deprivation, and learned helplessness. One model that is seen as having high validity on each of these parameters involves a more complex psychosocial stressor in male tree shrews, which have very strong territorial instincts. By confining two male tree shrews in one cage, a stable dominant–subordinate relationship is produced, with the subordinate shrew displaying stress-induced behavior and physiological correlates from the outset [34,36–38].

VI Effects of stress on glutamatergic neurotransmission in the hippocampus

Glutamate is the main excitatory synaptic neurotransmitter. It is produced in the central nervous system, primarily through glucose metabolism [39], and extracellular glutamate levels are closely regulated. Glutamate is key to such attributes as learning and memory, which are dependent on neuroplasticity, and it is also increasingly being suggested that it is a major neurotransmitter in many of the behavioral and physiological features that characterize mood disorders [40]. Its role in the effects of stress on the hypothalamic–pituitary–adrenal axis has been established [35], and it has also been shown to be involved in stress-induced changes that occur in the hypothalamus [41].

Stress has also been shown to cause an increase in extracellular levels of glutamate in the hippocampus of rats. Acute stress has been shown to be accompanied by a rise in extracellular glutamate levels, but levels rapidly returned to normal [42]. However, chronic stress produces a sustained increase in glutamate levels [35]. Furthermore, in rats previously exposed to chronic stress and then given an acute stress challenge, glutamate levels remained elevated rather than returning to normal at the withdrawal of the chronic stress, suggesting that chronic stress interferes with the usual mechanisms that regulate stress-related glutamate release [35]. This regulation is by means of glutamate transporter proteins [43,44], which have also been found to be increased in parts of the hippocampus in rats exposed to chronic stress, specifically in the CA3 region, where stress-induced dendritic remodeling has also been demonstrated in animal models [36].

VII Structural changes

The hippocampus is sensitive to stress in part because of its high expression of glucocorticoid receptors. Stress and depression are both associated with reduced hippocampal volume, but the hippocampal changes are not global. A high-resolution MRI study of depressed patients has suggested that the subiculum, but not the remainder of the hippocampus, is reduced in volume in depressive disorder [45]. Two major changes occur. First, there is dendritic atrophy in the pyramidal neurons with decreased dendritic branching of the dendrites [36,46]. This has the effect of reducing the number of functioning synapses on each neuron. Secondly, there is decreased neurogenesis in the dentate gyrus, an area in which new neurons continue to be produced in adulthood and appears to be strongly inhibited by stress and depression in animal models [36,47,48]. This may in part explain the impairments of memory, attention, and problem solving that are common symptoms of depressive illness. It is likely that the reduced hippocampal volumes seen in imaging studies in depressed patients are, at least in part, the result of dendritic changes and reduced neurogenesis [2,5,48].

In some studies of patients with major depression, hippocampal volume has been shown on MRI studies to be reduced compared with healthy controls, with the volume negatively correlated with the total time depressed and with the number of depressive episodes [49, 50]. However, these find-

ings have not been replicated in all studies. These inconsistencies might be a result of differing pathogeneses of depression in the patients studied; for example, one study found reduced hippocampal volumes in depressed women who had had early-life trauma but not in those who had not [51]. Studies of changes in the amygdala, which mediates behavioral responses to fear and strong emotion, an area important for the acquisition and storage of emotional memories and for mediating physiological and behavioral responses to fear and strong emotions, show a reduced number of cells and reduced neuronal activity (as assessed by measurements of blood flow and glucose metabolism) [8]. Some studies have shown an increase in the concentration of dendrites [5].

Post-mortem studies of the prefrontal cortex show reduced density and size of neuronal and glial cells, which is the likely explanation for the reduced volume seen in imaging studies [10,52].

VIII Modulation of stress-induced changes in the glutamate system

Effects of tianeptine on preventing stress-induced impairment in LTP

The best studied mechanism of cellular plasticity is LTP, which refers to the strengthening of synapses brought about by repeated stimulation [23,53,54]. LTP mediates learning and memory is largely dependent on glutamatergic neurotransmission for its induction, and is impaired by exposure to stress [16,55]. There is evidence from animal studies that the impairment in LTP is seen in unavoidable stress situation, but not in stress situations that can be controlled [56].

Acute administration of tianeptine has been shown to prevent the impairment in stress-induced LTP in the hippocampus for up to 2 hours. Tianeptine similarly blocks the effects of stress on amygdala morphology and synaptic plasticity [57] and the prefrontal cortex [27]. To a lesser extent, fluoxetine has a similar but shorter (1 hour) effect in the prefrontal cortex [27].

Effects of tianeptine on inhibiting glutamate-dependent stress-induced changes in hippocampal morphology

In animal models of depression, tianeptine has been demonstrated to reverse the effects of stress on hippocampal morphology. For example, in rats subjected to prolonged daily restraint or daily corticosterone injection

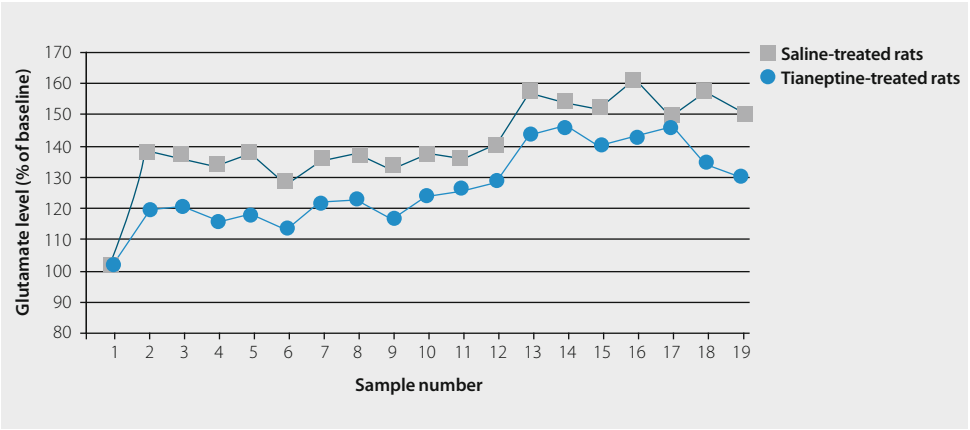

Figure 2. In an experiment by Reagan, Yamamoto and McEwen, rats were subjected to chronic restraint stress (over 21 days) and given daily administration of saline or tianeptine (10 mg/kg). Two days later, the animals were subjected to repeated acute restraint stress and measurements of glutamate levels were taken. Stress-induced increases in extracellular glutamate were returning to baseline more rapidly in the tianeptine-treated rats than in the saline-treated rats [35].

as a stress paradigm, the length and branching of apical dendrites of the hippocampal CA3 neurons was reduced. Injection of tianeptine before the daily stressor prevented these changes [58,59]. Established changes in hippocampal morphology caused by 3 weeks' exposure to the stress model may also be reversed by tianeptine [59].

Effects of tianeptine on inhibiting stress-induced changes in glutamatergic neurotransmission

Tianeptine modulates glutamatergic neurotransmission and acts to inhibit or reverse stress-induced neurological changes in the hippocampus, such as decreased dendritic branching, reduced neurogenesis in the dentate gyrus [2], increased extracellular glutamate levels (Figure 2) [60], and increased glutamate transporter expression (Figure 3) [60].

IX Clinical implications

The major classes of antidepressants developed in the second half of the 20th century (first the monoamine oxidase inhibitors, then the tricyclics, and most recently the SSRIs) are broadly equally effective clinically. Each subsequent class has been generally preferred over its predecessors because of an improved safety profile and a lower incidence of troublesome side

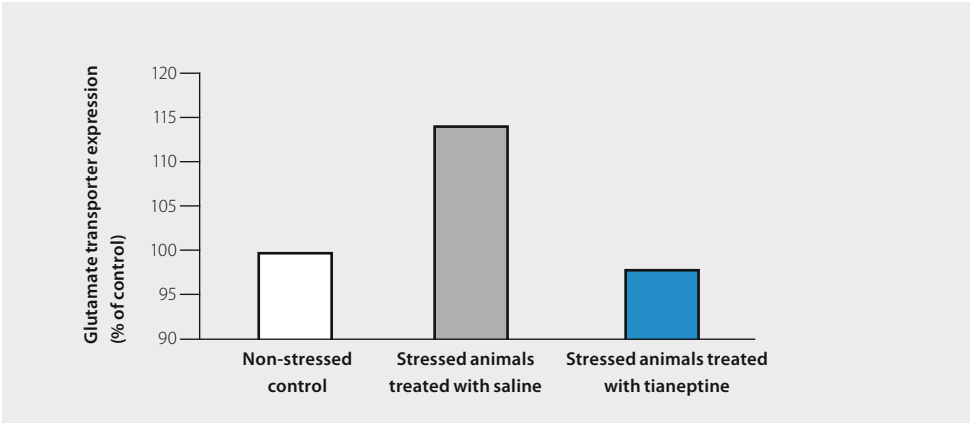

Figure 3. Glutamate transporter expression in the CA3 region of the hippocampus of non-stressed controlled rats given saline and of rats subjected to chronic restraint stress given saline or tianeptine. The stress-mediated increases in transporter expression were prevented by tianeptine [35,60].

effects, but the response rate to pharmacological therapy has remained largely unchanged, at about 65%, for nearly 50 years [61]. Moreover, with all these classes of drug there is usually a delay of several weeks before a therapeutic antidepressant response is seen [62] – a significant problem in a serious condition affecting a vulnerable patient group. This delay is despite the fact stable, therapeutic plasma and cerebral concentrations of these drugs are achieved within a week of treatment being started. Therefore, the clinical efficacy of these agents cannot be due solely to their immediate effect of increasing monoamine neurotransmitter bioavailability (an effect that all three classes have in common, although it is achieved by different mechanisms); rather, it is likely that their clinical efficacy is the result of adaptive neurobiological changes reflecting a neuroplastic response to therapy [61].

Further evidence that the clinical efficacy of antidepressant medication is not predicated on the basis of any effect on monoamine levels per se is provided by certain features of the drug tianeptine compared with these three main classes of antidepressants, as well as a more rapid onset of clinical effect. Tianeptine is a glutamatergic system modulator, whereas the mechanism of action of most antidepressants is reported to be an increase in levels of bioavailable serotonin or other monoaminergic

neurotransmitters. Nevertheless, it has been shown in multiple clinical trials to be at least as effective as SSRIs, the currently most widely used class of antidepressants [63,64]. This provides further evidence it is unlikely that the effects of these drugs on monoamine levels are the primary cause of their efficacy.

A further interesting and consistent clinical observation of treatment with tianeptine is that its onset of clinical antidepressant effect occurs markedly sooner after starting treatment than is the case with most antidepressants. For example, a 6-week, double-blind study of tianeptine (37.5 mg/day) vs the SSRI fluoxetine (20 mg/day), which assessed 178 patients with major depressive disorder for the first signs of improvement with therapy, found that after 7 days, significantly fewer patients in the tianeptine group than in the fluoxetine group were "extremely or severely ill" (16.1% vs 28.6%, p=0.046). Similarly, after 14 days, significantly more patients in the tianeptine group than in the fluoxetine group were described as "not ill at all" or "borderline" (21.8% vs 9.9%, p=0.029) (Figure 4) [65,66].

Using the Montgomery–Åsberg Depression Rating Scale (MADRS), a 10-item rating scale for severity of depression that is designed to be particularly sensitive to the effects of treatment on individual items [67], the study further looked at the timing of onset of any improvement in specific symptoms. The largest differences between the two treatment groups were in the fields of concentration difficulties and inner tension, two common symptoms of depression, both of which showed improvement significantly earlier with tianeptine than with fluoxetine (Figure 5).

X Conclusions

Neuroplasticity provides a novel approach both for the study of depressive illness and, through this, for the development of pharmacotherapeutic agents that target the pathophysiological mechanisms that underlie depression more directly than current therapies generally do. Indeed, it is becoming clear that some atypical antidepressants, and particularly tianeptine, promote and restore neuroplasticity and cellular resistance to the neuropathological changes that accompany depression, thereby preventing functional and structural alterations that increase vulnerability to depression and promote its progression [68].

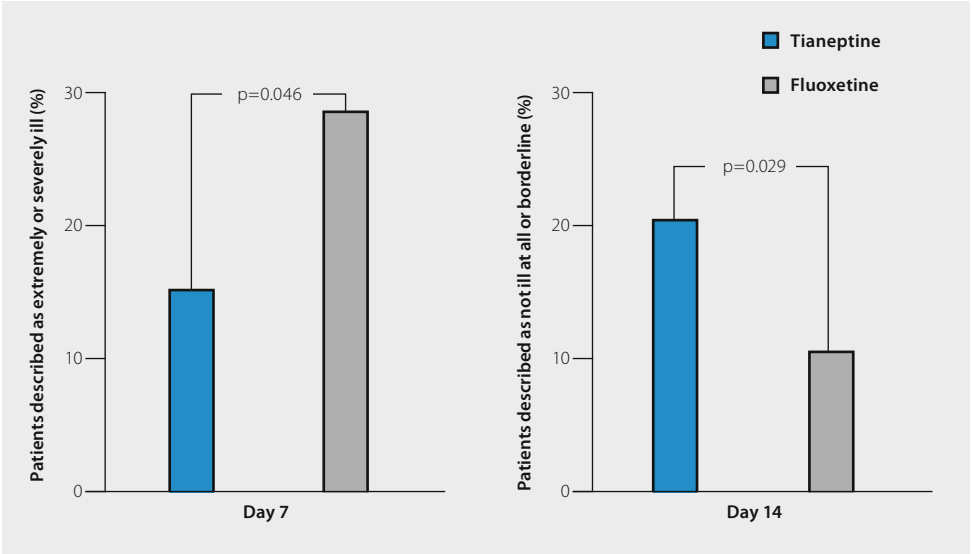

Figure 4. Comparison of the effects of tianeptine (37.5 mg/day) and fluoxetine (20 mg/day) in 178 patients with major depression at day 7 and at day 14 of treatment [65,66].

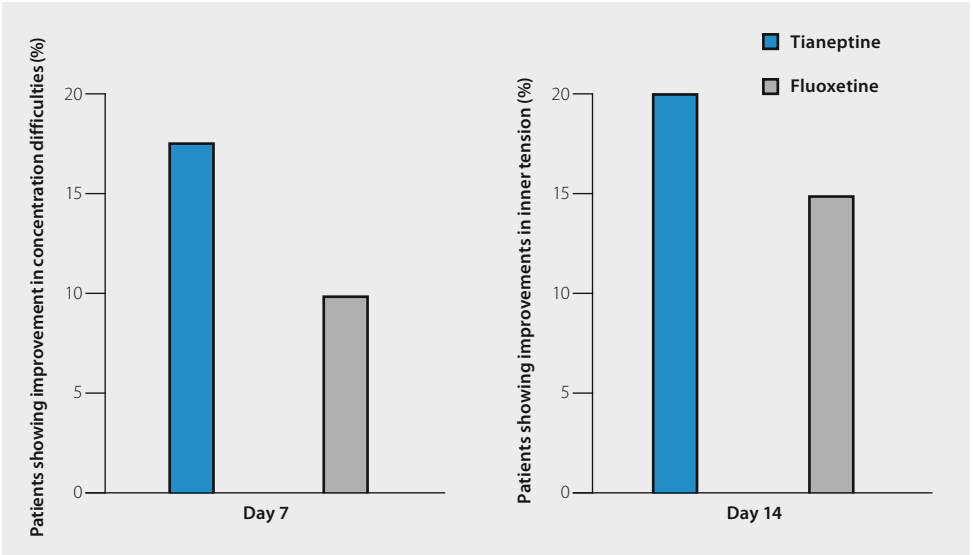

Figure 5. Comparison of the timing of improvement in two common symptoms of depression (concentration difficulties and inner tension) in 178 patients with major depression randomized to receive either tianeptine (37.5 mg/day) or fluoxetine (20 mg/day).

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CLINICAL CONSEQUENCES OF THE ROLE OF GLUTAMATE AND NEUROPLASTICITY IN DEPRESSIVE DISORDER

Philip Gorwood

I Introduction

Convergent and compelling data exist showing that glutamatergic modulation forms the basis of the effect of antidepressants in major depressive disorder, through its impact on neuroplasticity. However, a significant part of available information is based on animal studies, preclinical works and clinical research, and therefore this hypothesis has to be challenged at a broader clinical level.

The relevancy of a biological model in mood disorders may indeed be assessed through its capacity to highlight some key clinical factors. Four of these features are proposed, and will be used to test the hypothesis that neuroplasticity, through glutamatergic modulation, represents a core aspect of mood disorders and their treatment. The first observation is related to the fact that stress is a very frequent trigger of major depressive episodes, anxiety regularly being co-morbid. The second tries to give meaning to the fact that there is a delay of 1–3 weeks before the onset of action of the majority of antidepressants currently available. The third concerns the other therapeutic approaches for major depressive disorder, such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), total sleep deprivation (TSD), psychotherapy or even physical exercise, as not all interventions in major depressive disorder rely on pharmacological compounds. Finally, the fourth feature involved the specific outcomes observed with major depressive disorder, especially the high frequency of relapse and lifetime recurrence.

II Relevancy of stress in the model of depression regarding the role of europlasticity

At a clinical level, work during the last 50 years (see, for example, Hardy & Gorwood [1]) has demonstrated that depressed patients report a three times greater incidence of stressful life events before the onset of their episode, and that subjects facing severe stressful life events have a six-fold increase in their risk of a major depressive episode. Stress is defined as requiring adap-

tive changes, which might facilitate the emergence of a major depressive episode in vulnerable persons. At a biological level, stress has a neurotoxic impact, mainly through the hypothalamic–pituitary–adrenal axis because of the neurotoxicity of cortisol, the hippocampus being especially sensitive. A bridge was recently proposed between these two approaches, as stress is indeed found both in excess before a depressive episode (in accordance with clinical findings), but also predicts brain changes in children, especially the hippocampus [2], compatible with the biological aspects of stress at a biological level.

The role of stress exceeds that of immediate stressful events concentrated in the 2 months prior to the episode, and the role of early life stressors should be taken into account, as these are associated with higher risk of psychiatric and mood disorders later in life [3]. For example, subjects who lost one of their parents during childhood, were abused or neglected, or had severe social childhood conditions have a higher risk of later depression [3]. Animal models of maternal care are informative, as the quality of maternal care of the pup is known to modify later stress responses and cognitive performance [4]. The role of neuroplasticity and hippocampal structure have been analyzed in this model. For example, Champagne et al. [5] observed shorter dendritic branch length and lower spine density in the CA1 cells of the hippocampus in adult offspring who received lower levels of licking and grooming from their mother. This type of model highlights the fact that the quality of maternal care during infancy, and probably other aspects of childhood, may have an impact on synaptic plasticity, explaining part of the patient's later vulnerability.

Another heuristic example of early social interactions concerns the use of a communal nest for pups, with three mothers keeping their pups together providing a socially stimulating environment. At adulthood, mice reared in the communal nest, compared to mice reared in standard nesting laboratory conditions, showed an increase in brain-derived neurotrophic factor protein levels and increased adult neuronal plasticity, as indicated by longer survival of BrdU-positive cells in the hippocampus [6]. It could be argued that the role of maternal care, as a significant risk factor for major depressive disorder, does not take into account the fact that women are more at risk than males. Interestingly, it has been recently demonstrated that maternal care modulates the

relationship between prenatal risk and hippocampal volume in women, but not in men [7]. Even though it relies on an animal model, thereby giving only indirect evidence, this study proposes an interesting aspect of the gender-specific effect of maternal care on the neurotoxic effect of stress on the hippocampus.

III The place of neuroplasticity in the delay before treatment efficacy can be observed

There are many available antidepressants, and clinicians usually evaluate the efficacy of the one being used after 2 weeks of treatment if rapid improvement is the priority (such as in severe cases or following hospitalization). This period can be increased to up to 4 weeks in cases where the risk of missing a positive but late response is considered more important.

But the inevitability of this 2-week delay before judging the efficacy of the prescribed antidepressant could be challenged. Indeed, the known mechanisms of action of selective serotonin reuptake inhibitors (SSRIs) – i.e. blocking the serotonin reuptake in order to have more available serotonin in the synaptic cleft – occur after only a few minutes or hours [8]. The dominant hypothesis about the efficacy of SSRIs is therefore that blocking the serotonin transporter is an initial trigger that ends up in acting upon a still unknown "biological common pathway". Neuroplasticity is considered as a candidate, as different antidepressants have a demonstrated capacity to enhance neuroplasticity, or even neurogenesis in the dentate gyrus subgranular zone of the hippocampus. More precisely, tianeptine was the first antidepressant to demonstrate that its antidepressant activity relies on the prevention of stress-induced changes in cerebral morphology such as the retraction of apical dendrites of hippocampal CA3 pyramidal neurons [9,10] and the increase granule cell proliferation [11]. These and other findings led to the formulation of the hypothesis that antidepressants could oppose stress-induced loss of neural plasticity by blocking or reversing the retraction of hippocampal neurons (neuroplasticity) and by increasing cell survival and function (neurogenesis).

Indeed, the adult mammalian brain retains neural stem cells that continually generate new neurons, and their proliferation, migration, integration and differentiation in active mature neurons could be time-consuming. The

extent to which these cells integrate into the hippocampal circuitry remains unclear but a recent study indicated that some of these cells extend axons to the CA3 region in 2 weeks [12], in accordance with the 2- to 4-week delay before the clinical efficacy of antidepressants is observed.

Stress-induced apoptosis on the one hand, and neuroplasticity and neurogenesis on the other, are mediated by adrenal steroids working in concert with *N*-methyl-D-aspartate (NMDA) receptors [13]. The impact of antidepressants could be rather specific, as stress-mediated increases in glutamate efflux in the basolateral nucleus of the amygdala were inhibited by the antidepressant tianeptine but not by the selective serotonin-reuptake inhibitor fluoxetine [14].

If neuroplasticity has a central role in the treatment of depression through glutamate neurotransmission, another important argument would be that a drug with glutamatergic affinity demonstrates antidepressive properties with a faster onset of action. The most convincing evidence comes from a randomized trial of an NMDA antagonist, ketamine, in treatment-resistant major depression. Subjects receiving ketamine showed significant improvement in depression, compared with subjects receiving placebo, less than 2 hours after injection, and the improvement remained significant throughout the following week, with a 70% positive treatment response [15]. Some authors conclude that ketamine leads to rapid, robust, and relatively sustained antidepressant effects in patients with treatment-resistant major depression [16]. A meta-analysis also proposed that D-cycloserine (DCS), a partial NMDA receptor agonist, is a useful target for translational research on augmenting exposure-based treatment via compounds that impact neuroplasticity. Therefore, directly targeting the NMDA receptor complex might lead to rapid antidepressant effects.

IV The role of neuroplasticity and glutamate in non-pharmacological treatments

ECT is one of the most efficient ways to treat severe and/or refractory depression, and TSD one of the fastest ways (although the improvement is unstable) to achieve remission. If glutamate had an important role in the relief of depressed mood through neurogenesis, it could be expected that glutamate plays a significant role in these two approaches. Some authors

focused on prefrontal brain regions, such as the dorsolateral prefrontal cortex, because glutamate had been observed to be decreased in these regions in severely depressed patients with melancholic features [17], a subpopulation considered to be more responsive to ECT. Indeed, the reduction of GLX (containing glutamate, glutamine and GABA) was normalized by ECT [17], and an increase of GLX was observed in the left amygdalar and cingulated regions in ECT responders [18,19]. ECT, therefore, seems to act similarly to ketamine administration in its way of affecting the glutamatergic system [20].

During TMS, the magnetic field induces an electrical current in superficial cortical neurons, which in turn results in neuronal depolarization. When used in the low-frequency range, repetitive TMS modulates brain activity, thereby modulating neuroplasticity in cortical circuits [21,22]. There is large inter-patient variability in clinical outcome of TMS and in induced changes in cortical excitability. Langguth et al. (2007) showed that clinical improvement was associated with an increase in intracortical inhibition, intracortical facilitation and a prolongation of the cortical silent period, suggesting that NMDA-mediated LTD and neuroplasticity induction are the most relevant biological factors behind repetitive TMS effects. Metabolic changes observed using proton magnetic resonance spectroscopy following high-frequency rapid transcranial magnetic stimulation (20 Hz) were more directly analyzed [24]. A single as well as a series of consecutive rapid transcranial magnetic stimulations affected cortical glutamate/glutamine levels, not only close to the stimulation site (left dorsolateral prefrontal cortex), but also in remote (right dorsolateral prefrontal cortex [DLCP], left cingulate cortex) brain regions. As for lower prestimulation glutamate/glutamine levels, a higher glutamate/glutamine increase was observed after stimulation, indicating that glutamate seems to have a pivotal role in the efficacy of TMS.

Ketamine administration and REM-sleep deprivation in cats lead to similar biological changes [25], raising the possibility that the therapeutic effect of TSD on major depressive disorder acts at least in part through the glutamate neurotransmission. Accordingly, in healthy controls, an increase of glutamine was observed in the pontine region in response to TSD [26]. More recently, TSD led to an increase in GLX and glutamine in the DLPC in a subsample of eight male patients, as detected using proton MR spectroscopy.

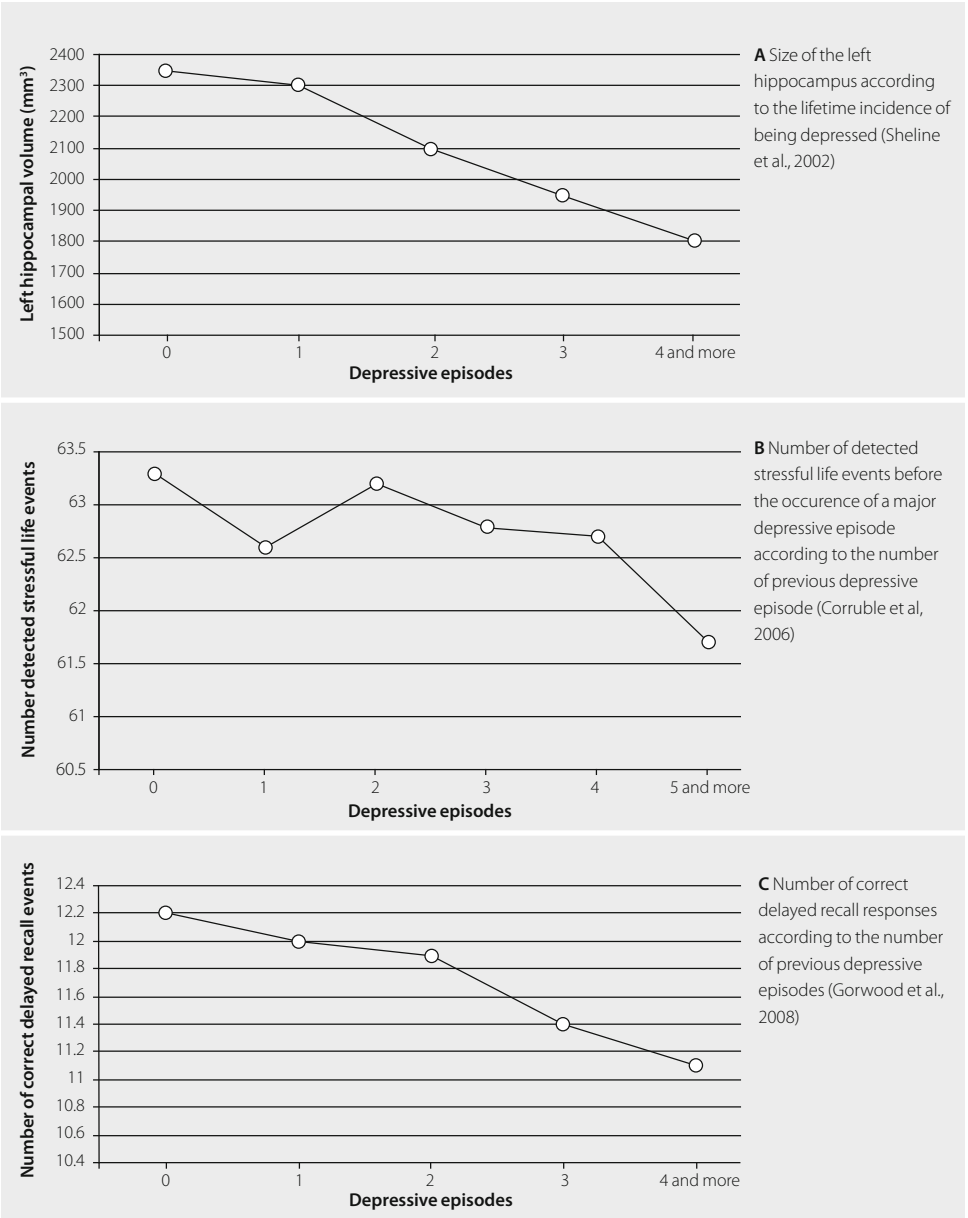
Structured psychological interventions are frequently used in major depressive disorder, sometimes with an efficiency that is perfectly comparable with antidepressants [27]. Although it is obviously difficult to demonstrate involvement of a neurotransmitter and of neuroplasticity in psychotherapy, some interventions, such as cognitive behavioral therapy (CBT) and interpersonal therapy (IPT) indeed alter brain metabolism in neural sites, consistent with these therapies' effects on mood and anxiety disorders [28].

Population studies have shown clear correlations between mental health and physical activity levels in both younger and older adults [29,30]. Endurance exercise may help to achieve a substantial improvement in the mood of selected patients with major depression [31], this approach being more frequently used, and with demonstrated efficacy, in elderly patients [32]. Exercise was associated with increased dendritic spine density, not only in granule neurons of the dentate gyrus, but also in CA1 pyramidal neurons and in layer III pyramidal neurons of the entorhinal cortex [33]. Therefore, the beneficial activity of exercise on mood disorder, either as an add-on or a specific treatment, might be obtained through its capacity to enhance neuroplasticity.

V Are depressive episodes neurotoxic?

Depressive episodes have a high risk of recurrence (around 50%), but a striking epidemiological finding concerns the variability of this risk according to the number of past episodes. Indeed, the 50% risk of recurrence rises to 70% for the risk of a third episode, while the risk of later episodes gets closer to 100% [34]. This pattern of risk is of the cumulative type, and is in accordance with the kindling hypothesis of depression (i.e., each episode increases the risk for the next one). The role of neuroplasticity has been tested in order to explain this "cumulative toxicity of depression on the hippocampus" hypothesis, using three types of studies, with convincing and converging results.

The initial finding is that of Sheline et al. [35], who showed that with more time spent with untreated depression during life, the size of the left hippocampus is reduced (Figure 1). The variability of this decrease between subjects is important, but the correlation between the time spent depressed and the volume of the left hippocampus is nevertheless impressive (r^2=0.34). Moreover, meta-analyses have confirmed that the total number of depressive episodes may be particularly correlated with hippocampal volume [36,37].



A Size of the left hippocampus according to the lifetime incidence of being depressed (Sheline et al., 2002)

B Number of detected stressful life events before the occurence of a major depressive episode according to the number of previous depressive episode (Corruble et al, 2006)

C Number of correct delayed recall responses according to the number of previous depressive episodes (Gorwood et al., 2008)

Figure 1. Three studies giving convergent evidence in favor of the "neurotoxicity" aspect of major depressive episodes, either directly, using **A** imagery [35] or **B** cognitive assessments [39], or **C** indirectly [43], showing the decreasing role of a precipitating factors with higher number of past episodes.

Some aspects of this neuroimagery finding linking depression and neurotoxicity have also been tested at a clinical level. The first study tried to compare the weight of stressful life events in a major depressive episode according to the number of past episodes. The hypothesis was that if patients are more fragile from having had many past episodes (or from spending a longer time of their life being depressed), then a smaller amount of stress could trigger a new episode. This hypothesis is usually described as the kindling hypothesis: repeated seizures in rodents require a lower and lower threshold of electric stimuli in the hippocampus, and this model is also observed in unipolar patients [38]. Accordingly, Corruble et al. analyzed a large sample of 13,377 treated patients with unipolar depression and found a linear decline of average stressful life event exposure for more frequent past episodes, even when age, gender and severity are taken into account [39]. The link between this study and Shelin's is made even more clear by the recent work from Kronmüller et al. [40]. In this study, a significant negative correlation was observed between major life events 3 months before the onset of depression and the left hippocampal volume for male patients. Therefore, severe stress does have a negative impact on hippocampus volume, especially in patients with past depressive episodes, and the size of the hippocampus is decreased in depressed patients, especially in patients who were depressed for a long period of their life. These different findings underline the importance of treating major depressive episodes quickly and efficaciously, not only to reduce the present burden impact of a depressive episode, but also to improve the long term impact of major depressive disorder, including risks of later relapses and recurrences. Antidepressants constitute an important way to modify the course of the disorder, with some antidepressants potentially having specific advantages. Indeed, it was shown in animal models that tianeptine can inhibit the stress-induced hippocampus volume loss [41] and block stress effects on memory [42].

The samples in imaging studies have often been fairly small, and potentially unrepresentative of the majority of outpatients with depression. We have been interested by measures of cognitive function that assay the function of the hippocampus, in order to check if these research findings could be replicated at a clinical level. Activation of the hippocampus has been observed with tasks such as word stem completion, success of word retrieval,

determining the emotional associations of words, or encoding. Even more consistent hippocampal activations have been shown in normal subjects with a paragraph encoding task. The latter involves encoding complex and integrated information, hypothesized to be a core role for the hippocampus and classically impaired in patients with known hippocampal lesions. Thus, there is considerable evidence supporting delayed paragraph recall as particularly related to hippocampal function in humans. We therefore included around 8,000 outpatients who fulfilled DSM-IV criteria for major depressive disorder according to the clinician, and analyzed their delayed recall during two visits, separated by 6 weeks. Following clinical response, at the second visit, the length of previous depressive history became more significant than current symptoms, even when age, educational level and profession were included in the model [43]. This study therefore supports the hypothesis that the length of past depression impairs memory performance, and favors the concept of toxic effects of depression.

VI Conclusions

Major depressive disorder is an extremely complex disorder, as it involves external social stressors and internal genetic vulnerability, and also since it can be helped by both pure pharmacological biological compounds and interpersonal psychotherapy. This is probably why the bio-psycho-social model of depression is so successful, helping to link different levels of analysis of the same phenomenon, rather than artificially distinguishing independent contributing factors.

The apparently opposite aspects of biology and psychology are in fact much more entangled than was initially thought. For example, the concept of gene x environment interactions (GxE) recently contributed to our understanding of why all subjects exposed to severe life events do not develop a depressive episode, and also favored connections between psychological and biological approaches to mood disorders. The role of neuroplasticity and neurogenesis could give meaning to many aspects of mood disorders, and especially for some of these that were rather obscure before the role of the antidepressant on neuroplasticity of the hippocampus was proposed by Duman, largely relying on the specific mechanisms of action of tianeptine [44].

Stress was mainly analyzed in the periods of time closely linked to the depressive episode, with information lacking (because of technical difficulties) regarding early major stressors. The animal model of "maternal care" proposed an interesting way of conceptualizing depression, the quality of grooming having a long-term impact on the structure of the hippocampus and the later risk of depressive behaviors. The role of neuroplasticity in the treatment of a depressive episode also sheds light on the long delay that occurs before clinical improvement can be observed. The fact that stem cells from the dentate gyrus require 2 weeks to reach the CA3 region of the hippocampus is interestingly very much in accordance with the clinical gap between the initiation of the treatment and the possible observation of efficacy. Interestingly, many different approaches in the treatment of depression involve glutamate and neuroplasticity, from ECT to physical activity, and from TMS to CBT. At a very clinical level, the important role of neurotoxicity (of depression) and neuroplasticity (of treatment) also give meaning to the typical outcome of major depressive episodes; i.e. the risk of later episodes being higher and the length of remission shorter with an increasing number of past episodes.

While avoiding the premature conclusion that the final biological pathway explaining depression has been found, it can be concluded that an important and relatively new aspect of depression is now clearly demonstrated, and that this new knowledge has many positive aspects, such as the possibility of developing specific drugs that might have a quicker onset of action in order to change the course of this disorder with considerable impact.

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